Language impairment in frontotemporal lobar degeneration

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SIGNED DECLARATION

I, Jonathan Daniel Rohrer confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

The term frontotemporal lobar degeneration (FTLD) describes a heterogeneous group of neurodegenerative disorders associated with frontal and temporal lobe atrophy. Within this spectrum, two progressive aphasia syndromes, progressive nonfluent aphasia (PNFA) and semantic dementia (SD), are well described. FTLD is commonly a genetic disorder and mutations in two genes, microtubule-associated protein tau (MAPT) and progranulin (GRN) account for a large proportion of familial cases.

A retrospective imaging study using cortical thickness measures shows involvement of the anteroinferior temporal lobes in SD and the left inferior frontal lobe/insula in PNFA. Studies of disease severity and of longitudinal imaging reveal spread through the left hemisphere and into the right hemisphere in both groups.

A genetics and heritability study shows that PNFA can be familial, although much less than the behavioural variant of FTLD, and that this is often due to mutations in GRN. Differing patterns of atrophy are shown between different genetic mutations and also between different pathologies with the same clinical syndrome.

Evidence from the neurological, neuropsychological, neuroanatomical, genetic and pathological features of the nonfluent aphasias suggests that there are at least three nonfluent aphasia syndromes: a disorder with motor speech impairment with or without agrammatism, a disorder with agrammatism but no apraxia of speech (found in patients with progranulin mutations) and a disorder without agrammatism or apraxia of speech but with word-finding pauses (consistent with descriptions of logopenic/phonological aphasia and pathologically associated with Alzheimer's disease).

Studies of specific deficits (single word processing, prosody, neologistic jargon, apraxia and behavioural symptoms) in the progressive aphasias provide further insight into the disease.

This thesis therefore provides neurological, neuropsychological and imaging data with related genetic and pathological information that can provide greater insights into the natural history and classification, and therefore pathophysiological basis of the neurodegenerative disorders that cause primary progressive language impairment.

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7. General conclusions: the progressive aphasias

7.1.1 Clinico-pathological and clinico-genetic associations in primary progressive aphasia. PPA as a syndrome has heterogeneous genetic and pathological associations. However, the importance of subtyping PPA is shown by the

third row of boxes which show in a schematic manner the pathological associations with SD, PNFA, LPA and with the familial GRN-associated form of PPA, where one pathological subtype tends to dominate. Each of the pathological subtypes are indicated by a separate coloured box: FTLD-TDP types 1 to 3 or type unclear if subtyping had not been performed, FTLD-tau (corticobasal degeneration, CBD; progressive supranuclear palsy, PSP; and Pick's disease), and Alzheimer pathology.

ABBREVIATIONS

ABA	Apraxia Battery for Adults
AD	Alzheimer's disease
AOS	Apraxia of speech
BSI	Boundary shift integral
bvFTD	Behavioural variant frontotemporal dementia
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CDR	Clinical Dementia Rating
CHMP2B	Chromating modifying protein 2B
CSF	Cerebrospinal fluid
FAB	Frontal Assessment Battery
FDR	False discovery rate
FTD	Frontotemporal dementia
FTD-MND	Frontotemporal dementia with motor neurone disease
FTLD	Frontotemporal lobar degeneration
FTLD-U	Frontotemporal lobar degeneration with ubiquitin-positive inclusions
FUS	Fused in sarcoma
GDCT	Graded Difficulty Calculation Test
GDST	Graded Difficulty Spelling Test
GNT	Graded Naming Test
GRN	Progranulin
FWHM	Full-width at half-maximum
LPA	Logopenic/phonological aphasia
MAPT	Microtubule associated protein tau
MMSE	Mini-mental state exam
MNI	Montreal Neurological Institute

MRI	Magnetic resonance imaging
PALPA	Psycholinguistic Assessments of Language Processing in Aphasia
PET	Positron emission tomography
PIQ	Performance IQ
PNFA	Progressive nonfluent aphasia
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
RMT	Recognition memory test
ROI	Regions of interest
SD	Semantic dementia
SPECT	Single photon emission computed tomography
SPM	Statistical parametric mapping
TDP/TARDP	Transactive response DNA-binding protein
UPDRS	Unified Parkinson's Disease Rating Scale
UPS	Ubiquitin-proteosome system
VBM	Voxel-based morphometry
VESPAR	Verbal and Spatial Reasoning Test
VCP	Valosin containing protein
VIQ	Verbal IQ
VOSP	Visual Object and Space Perception
WAIS-R	Wechsler Adult Intelligence Scale - Revised

1. Introduction

Acquired impairment of language in humans is most commonly seen as a result of stroke but over the last thirty years it has been recognized that neurodegenerative disorders can also cause an aphasia (Warrington, 1975; Mesulam, 1982; reviewed in Grossman et al, 2004; Hodges et al, 2007). The aim of this thesis is to study the group of patients who present with progressive language impairment from a number of different aspects: the clinical and neuropsychological features, the neuroanatomy, and the genetic and pathological causes of the disorder. This introductory chapter starts with a discussion of the clinical syndromes in which aphasia can be a presenting syndrome of neurodegenerative disease, namely frontotemporal lobar degeneration (FTLD) and primary progressive aphasia (PPA). In particular, the two most well-defined aphasia subtypes, semantic dementia (SD) and progressive nonfluent aphasia (PNFA) are introduced and defined. A simple model of language production is presented to understand the linguistic deficits that occur in FTLD and PPA, before comparing these disorders with the features that occur in the more common acute stroke aphasias.

Progressive language impairment as a primary feature of neurodegenerative disease was initially described by Pick in the late 19th Century (Pick, 1892) and such cases continued to be described intermittently in the early 20th Century. However, recent decades have seen a resurgence of research in this field. In a series of studies, Mesulam described a group of patients with "primary progressive aphasia" (PPA) who had a variety of different impairments of language (Mesulam, 1982; Mesulam, 2001; Mesulam, 2003). Independently, in the mid 1970's Warrington described patients with progressive impairment of semantic memory (Warrington, 1975), which was later to be called semantic dementia (Snowden et al, 1989). Although language impairment dominated the presentation in these groups it was observed that many of these patients later developed behavioural features similar to the disorder frontotemporal dementia (Snowden et al, 1992) and hence in the "Neary criteria" of 1998 (Neary et al, 1998) the term 'frontotemporal lobar degeneration' (FTLD) was introduced to cover three disorders: the behavioural syndrome of frontotemporal dementia (FTD or behavioural variant FTD, bvFTD) and two syndromes presenting with language impairment, namely progressive

nonfluent aphasia (PNFA), a disorder of speech production with agrammatism, and semantic dementia (SD), a disorder of semantic knowledge which commonly presents with fluent aphasia and loss of vocabulary. The overlap of the progressive aphasias with FTLD was noted to be not just in terms of the clinical syndrome but also in terms of the underlying pathology (Neary et al, 1998; McKhann et al, 2001; Mackenzie et al, 2007).

PPA is a relatively rare disorder but there are no large epidemiological studies and so it is unclear exactly how common it is as a syndrome or the relative preponderance of the PNFA and SD subtypes within the overall PPA or FTLD spectrum. PPA may be familial, particularly when the underlying syndrome is PNFA and this is discussed in detail in Chapter 4. The non-genetic risk factors for PPA are unclear although one study has shown an increased frequency of learning disability in patients with PPA and their first-degree relatives (Rogalski et al, 2008).

Speech and language pathways: where they can go wrong

The linguistic deficits seen in PPA as in other aphasia disorders can be understood by identifying where the normal speech and language pathway (Levelt et al, 1999) can go wrong. In a simple model of language production, the key stages include:

1. Generation of verbal thought
2. Semantic knowledge: the knowledge of concepts including the meaning of words
3. Word retrieval
4. Phonology: the selection and ordering of individual sounds into syllables and words
5. Grammar: the ordering of words at the level of phrases and sentences, including the use of 'function words' (articles, prepositions and conjunctions)
6. Motor programming: phonetics, articulation and prosody

Each of these stages can go wrong to cause a different language deficit and often multiple levels of deficit occur in the same syndrome.

1. Generation of verbal thought

Many patients with neurodegenerative disease participate less in conversations as a non-specific result of reduced facility with language but in some cases a reduction in propositional

speech can be the primary impairment where the patient seems literally to have 'nothing to say'. This problem has been called dynamic aphasia (Luria et al, 1967; Costello et al, 1989; Robinson et al, 1998; Warren et al, 2003; Robinson et al, 2006) and such patients are thought to have a selective deficit at the level of the generation of verbal thought: although the amount of speech is reduced, the sense and structure of the message (provided it can be generated in the first place) usually remain intact. Sentence generation is dependent on context: a patient may be able to describe a simple picture but may not be able to talk about an everyday topic or may provide a sparse (but error-free) description of a complex scene. Compared to this decreased spontaneous output, speech can be produced relatively normally in specific contexts, such as naming tasks, repetition or reading. A similar decrease in speech output occurs in many patients with frontal and subcortical deficits who exhibit a generalized inertia and slowing of thought. However in pure dynamic aphasia there is retained ability to generate novel non-verbal material such as song, suggesting that dynamic aphasia is a true language disorder and not simply a consequence of abulia (Warren et al, 2003). This syndrome is probably relatively rare and is generally not thought of as one of the key PPA syndromes.

2. Semantic knowledge

Some patients lose the ability to access the meaning of words i.e. their verbal semantic knowledge. This is usually evident as a deficient vocabulary with the patient using approximate or imprecise expressions (circumlocutions) that substitute for a single word (e.g. 'the thing', 'the whatchamacallit'), and speech (though fluent) may seem vague and lacking in substance. Errors of meaning or 'semantic paraphasias' may be evident as context-inappropriate words (for example, 'dog' may be used when 'pig' is meant). Superordinate or descriptive terms (such as 'animal') are used rather than more specific ones (such as 'squirrel' or 'lobster') and often accompany the use of circumlocutory phrases in an attempt to compensate for the deficiency of verbal knowledge. (It should be noted that 'semantic paraphasias' do not occur just in patients with semantic impairment but occur in any patient with word-finding difficulty.) There may also be increased reliance on stereotyped expressions, stock phrases and clichés. Such fluent but ultimately empty speech is characteristic of conditions in which there is damage to the verbal knowledge store, the paradigm for which is SD (Warrington 1975, Snowden et al,

1989; Hodges et al, 1992). In this situation the patient is usually anomic and has impaired comprehension of single word meaning.

3. Word retrieval

Some patients have difficulty retrieving words from the lexicon despite evidence that comprehension of the meaning of words (i.e. verbal semantic knowledge) is well preserved. In this situation there may be prolonged word-finding pauses affecting both spontaneous discourse and naming. This occurs in typical amnestic Alzheimer's disease (AD) and may occur relatively early in the disease (Bayles et al, 1987; Emery, 2000).

4. Phonology

Impaired phonological structure manifests as speech sound errors, or 'phonemic ('literal') paraphasias' at the level of individual words and syllables, most commonly substitutions ('crabon' for 'crayon'), transpositions ('aminal' for 'animal'), omissions ('elphant' for 'elephant') or additions ('hippopototamus' for 'hippopotamus') (Duffy, 2005). Such errors often first appear and remain more evident with polysyllabic words. This is seen in the PNFA syndrome and may be a very early symptom (Neary et al, 1998).

5. Grammar

Impaired grammatical structure (agrammatism) typically manifests as disjointed or 'telegraphic' speech composed of single words and short phrases, omitting function and connecting words (e.g. 'bird sat branch'). Incorrect ordering of words may occur, grammatical elements such as plurals or tenses may be misused or binary grammatical alternatives (such as 'yes-no', 'him-her') may be confused (Frattali et al, 2003). As with phonological deficits, this is also seen in the PNFA syndrome and is generally considered one of the primary features of this disorder (Neary et al, 1998).

6. Motor programming of speech: phonetics, articulation and prosody

Impairment at any of the levels detailed in 1-5 above is generally considered an aphasia i.e. an impairment in language. However, impairments later in the speech pathway i.e. in motor

programming usually affect the volume, rate, rhythm and intonation rather than the content of speech. The dysarthrias are disorders of articulation and usually caused by disease outside of the cortex i.e. extrapyramidal disease and with cerebellar and subcortical (pseudobulbar or bulbar) pathologies. However, cortical disease can also cause impairment of articulation: apraxia of speech (AOS) is a term that has been used to describe a motor speech disorder which (by analogy with other 'apraxias') can be defined operationally as impairment of the motor gestures of speech that is not attributable to a primary motor deficit (Darley, 1969; Croot, 2002; Ogar et al, 2005). Although the cognitive basis of AOS remains controversial, it is likely to arise at the level of cortical programming of phonetics, the step in speech production where the phonological structure is converted into an 'articulatory score' that directs the relevant muscles of the vocal tract to produce the word or phrase. AOS is probably therefore synonymous with phonetic breakdown or disintegration. The characteristic features of AOS are slow speech rate with hesitancy (difficulty initiating utterances), effortfulness (with articulatory groping, i.e. multiple attempts at trying to get to the right word and self-correction, worse with longer words), phonetic errors (errors in the shaping and timing of individual syllables) and dysprosody (abnormal rhythm, stress and intonation, partly attributable to poor phonetic sequencing) (Dabul, 2000; Croot, 2002; Duffy, 2005; Ogar et al, 2005; Duffy, 2006). Patients may describe the problem as a stutter or stammer. AOS is seen in the PNFA syndrome and although it was included as a supportive diagnostic feature in the Neary criteria (Neary et al, 1998) other studies have considered it a primary feature of the syndrome (Gorno-Tempini et al, 2004a; Josephs et al, 2006).

Other components of the motor programme that are functionally separate from phonetic encoding can also be disrupted by neurodegenerative disease: a key example is prosody, the intonational pattern of pitch, stress and timing that constitutes the 'melody' of speech (Ross, 1981). Many patients with speech-production difficulties lose the normal rhythms of conversational speech and the ability to regulate fine pitch and accent shifts. If severe, dysprosody may disrupt the intelligibility of the utterance as a whole and could be misinterpreted as a primary verbal problem. Commonly, dysprosody is secondary to poor

articulation (e.g. in PNFA) but rare cases of primary progressive dysprosodia have been described (Confavreux et al, 1992; Ghacibeh et al, 2003).

Summary of clinical features in PNFA and SD (Table 1.1)

The characteristic features of PNFA are the presence of agrammatism and hesitant, effortful speech secondary to apraxia of speech. Spontaneous speech is therefore nonfluent with the presence of sound errors (phonetic and phonemic) (Weintraub et al, 1990; Tyrrell et al, 1991; Turner et al, 1996; Westbury et al, 1997; Neary et al, 1998; Gorno-Tempini et al, 2004a; Ogar et al, 2007). Most patients will eventually become mute. Other features include anomia that is initially mild with a suggestion that verb naming may be affected more than nouns (the opposite pattern to that seen in SD: Hillis et al, 2002; Hillis et al, 2004a). The underlying cognitive deficit causing anomia has not been completely clear in PNFA and although there is some evidence that a primary word retrieval deficit is implicated this may not be the only or primary domain (Rogalski et al, 2008). Semantic knowledge and single word comprehension are essentially normal early in the disease but usually become affected a number of years into the illness (Blair et al, 2007). The cause of impaired single word comprehension in PNFA as the disease develops is also unclear although there have been reports of patients with very early processing deficits in the comprehension pathway of an auditory agnosia (Uttner et al, 2006). As well as the expressive agrammatism seen in PNFA, patients also have receptive agrammatism and a sentence comprehension deficit (Cooke et al, 2003; Grossman et al, 2005a; Peelle et al, 2007). Patients perform poorly on complex sentences but relatively normally with simple sentence structures. Patients with PNFA have an early difficulty with repetition of polysyllabic words and sentences. This progresses such that later in the disease even monosyllabic word repetition becomes difficult. The impaired polysyllabic word repetition compared to intact single word comprehension has been suggested to be a simple bedside measure for distinguishing the nonfluent aphasias from SD e.g. asking the patient to repeat hippopotamus and then point to which is the picture of the hippopotamus (Hodges et al, 2008). Patients with PNFA often have a phonological dyslexia and writing may be agrammatic with phonological errors although this tends to be affected later than speech.

Non-linguistic cognitive domains can also be affected in PNFA e.g. calculation and limb praxis (Joshi et al, 2003). Episodic memory is relatively intact in patients with PNFA as are visuospatial and visuoperceptual skills. Although language impairment is the dominant feature early on in the disease patients may develop behavioural features similar to the behavioural variant of FTLD as the disease progresses. Early on this may be a co-existing depression (Medina et al, 2007) but later there may be apathy, anxiety or irritability (Marczinski et al, 2004; Rosen et al, 2006; Banks et al, 2008). Neurological examination may reveal a parkinsonian syndrome or more rarely motor neurone disease.

The characteristic features of SD are anomia and impaired single word comprehension secondary to a deficit in verbal semantic knowledge. Spontanous speech is relatively fluent but empty in content and circumlocutory with semantic errors. There is loss of the use and understanding of words that were formerly in the patient's vocabulary. The underlying deficit is in semantic knowledge and as the disease progresses deficits in non-verbal domains develop, the most common being an associative visual agnosia (Bozeat et al, 2000; Adlam et al, 2006). Patients also have a surface dyslexia i.e. a difficulty in reading 'irregular' words (which they regularize e.g. reading pint as rhyming with mint) and this is also due to loss of verbal semantic knowledge. Behavioural symptoms are more common in SD than PNFA with patients often developing disinhibited behaviour or changes in appetite behaviour as the disease progresses (Snowden et al, 2001; Rosen et al, 2006). Neurological examination is usually normal in patients with SD.

Table 1.1

Summary of clinical features of SD and PNFA

	PNFA	SD
Spontaneous speech	Slow with hesitancy, effortfulness secondary to motor speech disorder and/or agrammatism Phonetic/apraxic errors Phonemic errors	Normal rate but fluent, empty and circumlocutory Semantic errors
Semantic knowledge/ single word comprehension	Initially intact but in late disease becomes affected	Impaired secondary to verbal semantic impairment
Word retrieval/naming	Initially can be normal but anomic as disease progresses	Anomia
Grammar/sentence comprehension	Impaired for complex sentences	Normal initially but becomes impaired as single word comprehension deteriorates
Single word repetition	Impaired with phonetic/apraxic errors	Normal
Sentence repetition	Can be impaired	Often normal initially but can make transposition errors
Motor speech impairment/apraxia of speech	Present	None
Reading	Phonological dyslexia	Surface dyslexia
Other cognitive domains involved	Can later develop dominant parietal impairment (dyscalculia, limb apraxia) particularly if associated with corticobasal syndrome	Non-verbal semantic impairment, can develop object agnosia/prosopagnosia
Behavioural symptoms	Depression, apathy	Disinhibition, appetite change
Neurological examination	Can be associated with a parkinsonian syndrome or rarely motor neurone disease	Usually none

Other phenotypes of language impairment in neurodegenerative diseas

Although PNFA and SD are the most common of the progressive language disorders, other disorders have been described. The rare disorders of progressive "dynamic" aphasia (probably secondary to a deficit at the level of generation of verbal thought: Warren et al, 2003) and progressive dysprosodia (a primary prosodic deficit: Confavreux et al, 1993; Ghacibeh et al, 2003) have been described above. A disorder which has been described as being relatively common by one research group is logopenic aphasia (more recently also called the logopenic/phonological variant of PPA, LPA), held to be secondary to a deficit in short term or working memory (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008; Wilson et al, 2009b). Less common phenotypes described include progressive anomia or non-fluent anomic aphasia where anomia is the initial symptom (Snowden et al, 2003; Snowden et al, 2007b; Pickering-Brown et al, 2008) or progressive mixed aphasia where features of both PNFA and SD occur early in the same disorder (Grossman et al, 2004; Alladi et al, 2007). Chapter 4 of this thesis investigates the heterogeneity of progressive language disorders in more detail.

Current investigation and levels of classification of progressive language impairment

The syndromes of progressive language impairment are currently described at a clinical level i.e. by the cognitive deficits seen during bedside cognitive testing and in particular neuropsychological assessment. This is mirrored in the current descriptive criteria for the disorders: the 1998 Neary criteria for FTLD (Neary et al, 1998) describe the features of PNFA and SD; the 2001 McKhann criteria for FTD (McKhann et al, 2001) merely describe a "language presentation of frontotemporal dementia" without specifying any subtypes; and the "Mesulam criteria" (Mesulam, 2001; Mesulam 2003) describe the features of "primary progressive aphasia", also without specifying any subtypes (and in this case separating the progressive language disorders completely away from the behavioural disorder of frontotemporal dementia). Although neuroimaging, particularly structural magnetic resonance imaging (MRI) or functional imaging (posititron emission tomography, PET, or single photon emission computed tomography, SPECT), have been used in the diagnostic process they currently only form a relatively minor part of criteria e.g. as non-specific supportive features in the Neary criteria. However, the feature of focal temporal lobe atrophy in SD has often led to it

being described at a neuroanatomical level as the "temporal variant" of FTLD by some research groups (e.g. Seeley et al, 2005). The neuroimaging features of the specific subtypes are described in more detail in Chapters 3 and 5. Beyond the clinical/neuropsychological and anatomical descriptions of the progressive aphasias it has been difficult to provide a comprehensive pathological or genetic level of classification for these disorders. Whilst most of the disorders that present with language impairment seem to have one of the proteinopathies considered to be a "FTLD pathology" i.e. a problem in either of the proteins tau or TDP-43, a minority of the patients have the same pathology as Alzheimer's disease (i.e. amyloid plaques and tau neurofibrillary tangles). This has led some groups to describe patients as having a "language presentation" of Alzheimer's disease, which is logically a different level of classification to describing a progressive language disorder as having PNFA, SD or one of the other clinical phenotypes. The underlying genetics and pathology of these disorders is described in Chapter 4.

Management of progressive language impairment

There are currently no symptomatic or curative pharmaceutical therapies for PNFA or SD. Some small trials have taken place without any clearly positive results (bromocriptine: Reed et al, 2004; galantamine: Kertesz et al, 2008) as well as a number of unsubstantiated single case reports of the use of a variety of drugs (Tobinick, 2008; Decker et al, 2008). Although there is no clear evidence base, many patients find speech and language therapy helpful to provide communication strategies: the use of Augmentative and Alternative Communication methods are little studied but low-technology input such as communication notebooks are generally favoured over more high-technology devices such as hand-held computers (Rogers et al, 2000; Beukelman et al, 2007). Genetic counselling is important in those with a family history and/or a known mutation.

A comparison of progressive language impairment with acute language impairment

Although there is considerable overlap between the vascular aphasic syndromes and the progressive aphasias, certain features are more typically seen in one setting rather than the other.

Anomia occurs in all aphasias: in aphasic stroke it commonly remains as an isolated deficit as recovery occurs (Kertesz et al, 1977) whereas pure anomia is rare (or rarely persists as an isolated feature) in degenerative disease, reflecting the progressive nature of the disease process.

Deficits of single word comprehension are characteristic of SD and are also common in acute lesions involving the anterior temporal lobe (notably herpes simplex encephalitis) (Warrington et al, 1984; Noppeney et al, 2007) and the posterior superior temporal lobe (Hillis, 2007). Category effects are more common in the acute setting (Lambon Ralph et al, 2003; Noppeney et al, 2007), perhaps because they require complete destruction of a discrete functional region, rather than the more diffuse and partial damage that attends degenerative pathologies. Fluent aphasia arising from acute damage involving the posterior superior temporal lobe (so-called 'Wernicke's area') (Wernicke, 1874) tends to be associated with less severe impairment of single word comprehension and more prominent phonological errors and neologisms ('jargon aphasia') than are observed in the fluent aphasias of degenerative disease.

Phonemic errors are seen both in acute ('Broca's aphasia') and chronic progressive (PNFA) settings, and are classically associated with nonfluent aphasia. Phonological breakdown often co-exists with agrammatism, so that patients with PNFA or with Broca's aphasia typically have telegraphic or 'agrammatic' speech and concurrent deficits at the level of sentence comprehension (Grossman et al, 2005a). Furthermore, just as PNFA is commonly associated with progressive AOS, so patients with a Broca's aphasia often have an accompanying AOS (Dronkers, 1996; Hillis, 2007).

Classically, 'transcortical' and 'conduction' aphasias are considered to arise from acute damage respectively involving the cortical 'centres' for speech comprehension and production or the anatomical pathways connecting these centres (Lichtheim, 1885). 'Transcortical' sensory and motor aphasias are associated with relative sparing of speech repetition despite defective comprehension and production, respectively (Goldstein, 1912). Conversely, the hallmark of

'conduction aphasia' (Lichtheim, 1885; Bartha et al, 2003) is a relatively selective deficit of speech repetition at the level of phrases, with relatively well preserved spontaneous speech, suggesting a disruption of the transfer of information between input and output speech pathways. These different patterns are generally observed as acute vascular syndromes, but transcortical motor aphasia has features similar to dynamic aphasia while transcortical sensory aphasia closely resembles the fluent aphasia of the SD syndrome, and conduction aphasia has been reported rarely as a presenting feature of neurodegenerative disease (Hachisuka et al, 1999). By analogy with the explanation proposed for the greater preponderance of semantic category effects in the acute setting, it is likely that the transcortical and conduction syndromes require relatively discrete damage that removes a nodal region or disconnects it from other regions in a functional network. These conditions are most likely to be met in acute vascular damage, rather than degenerative disease, in which there is greater potential for incomplete damage involving a number of cortical regions and their functional connections

These observations raise the more fundamental issue of the basis for the observed dissimilarities between acute vascular and degenerative aphasic syndromes. To the extent that the acute and progressive aphasic syndromes both illustrate the effects of interruption of distributed functional networks, the acute and progressive aphasias are predicted to share certain phenomenological similarities. The many divergences between the progressive and acute syndromes of language breakdown illustrate the effects of chronic, evolving damage distributed amongst functionally connected brain areas, versus the acute failure of a single network component. The vascular anatomy of the human language cortices means that certain syndromes are intrinsically more likely (for example, jargon aphasia due to focal posterior superior temporal lobe damage) or less likely (for example, semantic disintegration due to anterior temporal lobe damage) to occur in the acute setting. Moreover, the degenerative aphasias result from subtotal damage simultaneously involving a number of cortical regions and their connections, and therefore in principle might have no precise acute analogue. In contrast to acute infarction, degenerative pathologies have the potential for continuing 'noisy' information processing within and between affected brain regions. Furthermore, it is likely that the microstructure of language networks is differentially affected by chronic diseases with

abnormal protein deposition in surviving cellular components, and by acute necrosis affecting all components in a region more or less uniformly.

Chapter 1 Summary

Progressive language impairment occurs as part of neurodegenerative disorders. The nosology of (and therefore terminology used in) these disorders is complicated. They have been included in the group of diseases known as frontotemporal lobar degeneration (FTLD) because of the known overlap clinically, genetically and pathologically with the more common disorder frontotemporal dementia which presents with behavioural symptoms (and is therefore sometimes known as behavioural variant frontotemporal dementia, bvFTD). However, other research groups have sought to separate them from bvFTD and create descriptive criteria solely for progressive language disorders, naming this primary progressive aphasia (PPA). It seems clear that whichever overarching spectrum of disorders they are included within (FTLD or PPA) there are multiple subtypes of progressive language impairment: the two most common are PNFA and SD but it is unclear how many other clinical/neuropsychological phenotypes there are. It is also clear that there is no one-to-one correlation between the clinical/neuropsychological phenotypes of progressive language disorders and the acute aphasias, which are more common and therefore generally better known to the neurologist and neuroscientist. It is important to reiterate, as discussed above, that progressive language disorders can be described at multiple levels of classification and that currently the clinical/neuropsychological phenotypic description is the most prominent. However, as there is no one-to-one clinico-genetic or clinico-pathological correlation, when it comes to entering patients into clinical drug trials using drugs targeting a particular protein or gene it will be important to be able to classify the disorders according to their underlying genetics and neuropathology. Neuroanatomical descriptions using particular neuroimaging techniques may provide an interface between clinical/neuropsychological phenotypes and genetic/pathological phenotypes.

This thesis sets out to answer some of these questions. The general hypotheses of the thesis are that:

1) There are multiple clinical subtypes of language impairment in frontotemporal lobar degeneration/primary progressive aphasia.

2) There are multiple pathological and genetic causes of the progressive aphasias and increasing knowledge of clinical subtypes will allow better clinico-pathological and clinico-genetic correlation.
3) Clinical subtypes are defined by their pattern of neuropsychological deficits, which map on to neuroanatomical patterns of cell loss. Changes in clinical and neuropsychological phenotype over time are paralleled by concurrent changes in the pattern and extent of atrophy over time.

Chapter 2 sets out the techniques and methods used in the thesis both from an imaging and neuropsychological perspective.

Chapter 3 aims to answer the questions: *what patterns of cortical cell loss are seen in the well-defined clinical subtypes of PNFA and SD and what is the change in atrophy over time?* The chapter uses a retrospective cohort of patients with PNFA and SD to define the neuroanatomical patterns of cell loss in these disorders using the relatively new technique of cortical thickness measurement. The same cohort is then explored with longitudinal volumetric measurements of rates of atrophy to look at patterns of change over time.

Chapter 4 aims to answer the questions: *what is the genetic and pathological basis of progressive aphasias and can investigation of the patterns of atrophy in defined genetic and pathological subtypes improve clinico-genetic and clinico-pathological correlation?* This chapter uses a retrospective cohort of patients within the whole FTLD spectrum, including patients with the behavioural variant FTD for comparison, who have had DNA samples or pathological specimens collected. The heritability of each subtype is examined and then patterns of atrophy are investigated in specific genetic and pathological subtypes.

Chapter 5 aims to answer the questions: *how many clinical subtypes of progressive aphasia are there and how do these map on to neurological features and on to specific genetic and pathological causes.* This chapter investigates a prospectively studied cohort of patients with a progressive aphasia from a clinical, neuropsychological and neuroanatomical perspective in

order to define specific subtypes. Case studies of two patients with genetically-defined disease and a case series of patients with a specific neurological syndrome are also presented.

Chapter 6 aims to answer the questions: *what do specific behavioural and neuropsychological deficits in the progressive aphasias tell us about the disease and how are they related to the underlying neuroanatomical pattern of cell loss?* Patients with progressive aphasia were studied prospectively to look at areas previously little studied in this group, namely single word processing, prosodic processing, the production of neologistic jargon, the presence of orofacial and limb apraxia and abnormal behaviour.

2. Techniques and methods

2.1 Imaging techniques

Brain image acquisition

All MR brain images were acquired on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI) using an inversion recovery-prepared fast Spoiled Gradient Recall acquisition (echo time = 5ms, repetition time = 12ms, inversion time = 650ms). T1-weighted volumetric images were obtained with a 24-cm field of view and 256 x 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane.

Cross-sectional volumetric measurement

Whole brain

A rapid, semi-automated technique of brain segmentation was performed for each scan using the MIDAS software package (Freeborough et al, 1997a). This involves interactive selection of thresholds, followed by a series of erosions and dilations, and yields a brain region which is separated from surrounding cerebrospinal fluid, skull and dura. This provides a whole brain volume measurement in millilitres.

Cerebral hemispheres

Left and right cerebral hemisphere volumes were calculated as follows. Scans and associated brain regions (generated in the whole brain segmentation step described above) were initially transformed into standard space by registration to the Montreal Neurological Institute (MNI) template (Mazziota et al, 1995) within the MIDAS software package. Left and right hemisphere MNI templates were created by dividing the MNI whole brain template along a line coincident with the interhemispheric fissure also within the MIDAS software package. Left and right hemispheric regions were thus defined in each scan by an intersection of each individual's whole brain region and the hemisphere MNI templates. This provided a measure of left and

right hemisphere volume and therefore also a measure of cerebral asymmetry by dividing one hemisphere volume by the other i.e. a left/right (or right/left) volume ratio.

Ventricles

Ventricular volumes were calculated using a semi-automated segmentation technique within the MIDAS software package. The volumes included the lateral ventricles and temporal horn of the lateral ventricles but not the third or fourth ventricle and were outlined on all sequential brain slices encompassing these regions.

Temporal lobes

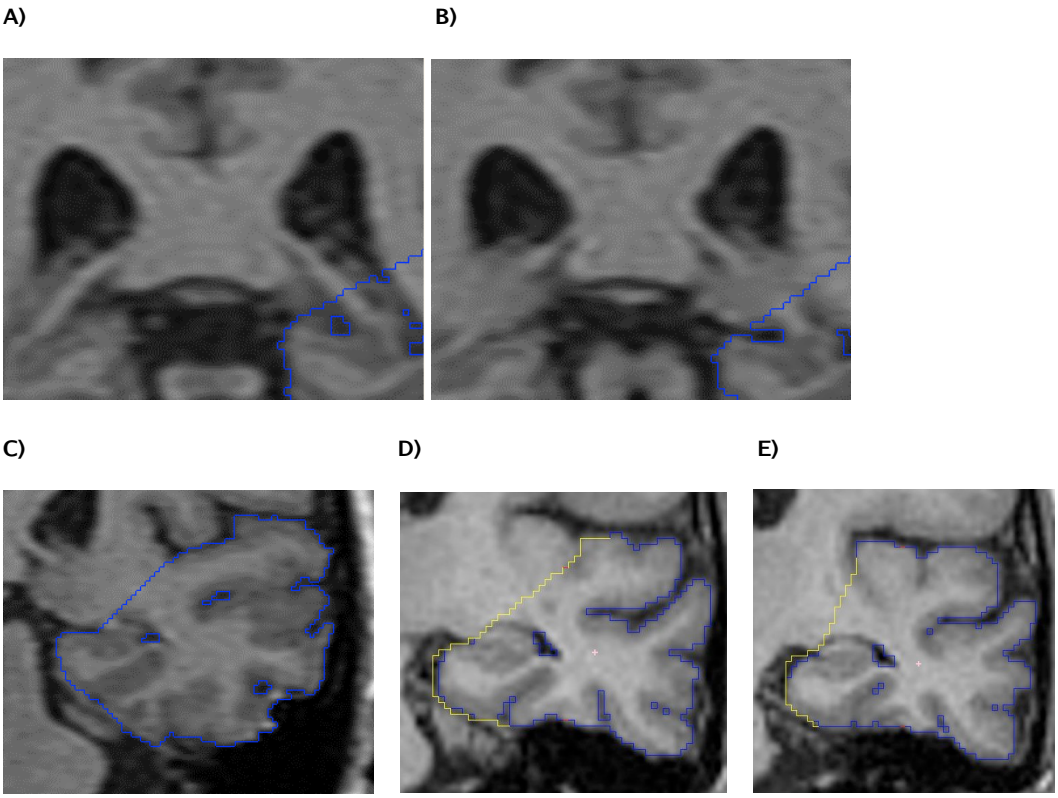
A technique for temporal lobe segmentation has previously been described (Chan et al, 2001b). The method used here is a variation on this with some changes made to improve accuracy. Trials on twenty scans during the pilot phase of the study revealed an intraclass correlation coefficient of 0.99 and an average segmentation time per temporal lobe of 30 minutes.

Initially each scan was reflected across the mid-sagittal plane, producing two scans, each a mirror image of the other. This enabled the temporal lobe to be consistently measured on the right hand side of the presented image, whether the temporal lobe was left or right. All the boundaries of the temporal lobe were traced around with two orthogonal views available. A consistent threshold of 60% of mean brain intensity was applied to exclude lower intensity voxels, which correspond predominantly to CSF. The caudal boundary was defined as the coronal slice where the thalamus and fornix first become distinct structures and is generally where the longest length of the fornix is observable (Figures 2.1.1A and 2.1.1B). An arbitrary cut off point was used for the temporal lobe stem, determined by a straight line connecting the most inferior and medial point of the Sylvian fissure to the superior lateral-most point of the medial temporal lobe, adjacent to the stem (Figures 2.1.1C). However, if this demarcating line clearly eliminated any subcortical structures then an alternative cut off was used. In these cases, a straight line was drawn from the same inferiormedial portion of the Sylvian fissure, now connecting to the most superior surface of the subcortical structure (i.e. hippocampus or

amygdala) after which the demarcating line followed the curve of this structure back to the superior lateral-most point of the medial temporal lobe. The accessory gyrus was included as soon as the CSF was just visible between the medial side and the temporal stem on the coronal view (Figures 2.1.1D and 2.1.1E).

Figure 2.1.1

Temporal lobe segmentation protocol: A) First slice i.e. caudal boundary at longest length of fornix, B) Second slice where the thalamus begins to obstruct the fornix, C) Standard cutoff of temporal stem from inferior-medial most point of Sylvian fissure to superior-lateral most point of medial temporal lobe, D) Slice before the accessory gyrus inclusion, E) Slice after the accessory gyrus inclusion.



Midbrain

Midbrain volumes were calculated using the MIDAS software package and a previously described segmentation method (Paviour et al, 2006): two orthogonal views were used to define a superior cutoff (upper border of the midbrain tegmentum in the mid-sagittal slice), an inferior border at the superior border of the pons in the mid sagittal slice, and anterior and

posterior borders defined by the brain tissue/cerebrospinal fluid boundary (interpeduncular cistern anteriorly and including the quadrigeminal plate).

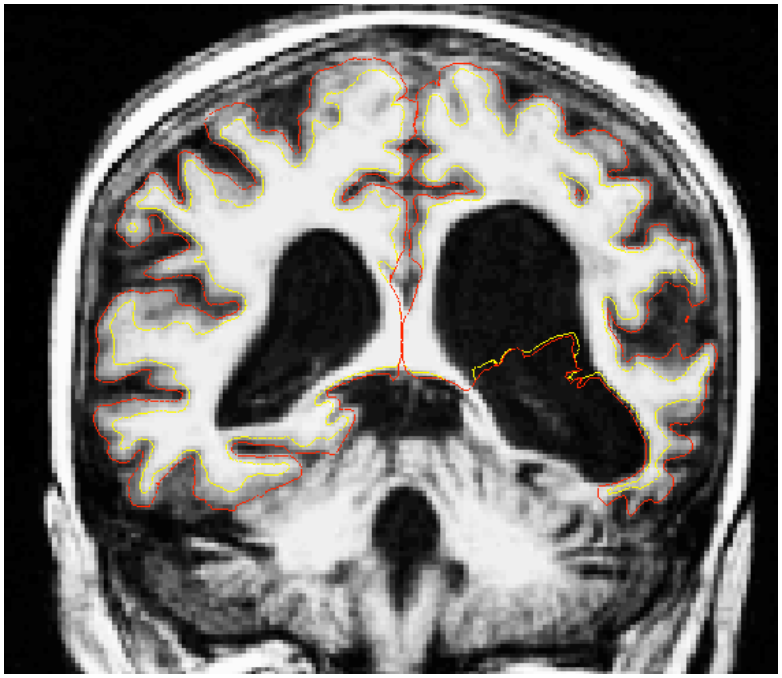
Cortical thickness

The measurement of cortical thickness in volumetric MRI scans is a relatively new technique (Dale et al, 1999; Fischl et al, 2000; Kim et al, 2005; Hutton et al, 2008). In neurodegenerative disease it has yet to be used extensively in investigating patterns of cortical cell loss and although the patterns seen using this technique are likely to substantially overlap with other techniques such as voxel-based morphometry (see below) it may be that it will provide complementary information (e.g. about areas that are difficult to assess using methods such as voxel-based morphometry) or be a more sensitive or specific measure of change.

In this thesis cortical thickness estimation was performed using the Freesurfer image analysis suite (Dale et al, 1999; Fischl et al, 2000), version 4.0.3 on a 64-bit Linux CentOS 4 Cluster managed by a Sun Grid Engine. This is a freely available set of software tools that can be downloaded from the internet (http://surfer.nmr.mgh.harvard.edu/) and is an automated process generating a measurement of cortical thickness. Initially registration of the scans to the Talairach atlas is performed followed by an intensity normalization step and then removal of non-brain tissue in each scan using a skull-stripping process. At this point, instead of the standard Freesurfer brain mask being used, this was replaced with the brain region made using the MIDAS software package as described above in whole brain volumetric methods (Freeborough et al, 1997a). An automated white matter segmentation is then performed followed by a surface tessellation and deformation process that creates an accurate grey/white boundary (white matter surface) and grey/CSF boundary (pial surface). The results of these surface reconstructions were visually inspected. During the initial trial phase of running Freesurfer it was noted that segmentations were poor if there was substantial atrophy, particularly around the lateral ventricles when they were large (Figure 2.1.2).

Figure 2.1.2

Poorly segmented scan during initial phase of Freesurfer cortical thickness pipeline



This problem was solved by incorporating the ventricle segmentations (that are generated in Freesurfer in its volume processing stream) into the white matter mask. Further visual inspection also revealed occasional misclassification of white matter, particularly in the temporal lobes. This was solved by a manual editing process available within Freesurfer where 'control points' can be added to define areas of white matter followed by re-running of the initial processing stream.

Cortical thickness can be estimated by computing the average shortest distance between the white matter surface and the pial surface. For group comparison, all subjects' cortical reconstructions (or rather an inflated model of them) are registered to a common spherical surface-based atlas. The data are smoothed using a surface-based Gaussian kernel of 20mm full width half-maximum. Parcellation of the cortex into different units based on gyral and sulcal structure is also performed (Desikan et al, 2006).

A vertex-by-vertex analysis using a general linear model was then performed to examine differences in cortical thickness between groups. The particular model used in each of the studies described in the thesis is shown in the chapter.

Voxel-based morphometry (VBM)

Voxel-based morphometry (VBM) is a computational neuroimaging technique that allows analysis of structural MRI scans to investigate differences in morphology (tissue density) between groups (e.g. where in the brain is there less grey matter density in a disease group compared to controls?) or the relationship of morphology to a behavioural or neuropsychological score (e.g. where in the brain does grey matter density correlate with naming score?). In comparison to region of interest methods VBM is essentially unbiased as all areas of the brain are considered.

The process of VBM consists of a number of steps:

1) Normalization or registration – this is a process where all scans are put into the same space so that they can be compared.
2) Segmentation – this classifies brains into grey matter, white matter and CSF.
3) Modulation – this process corrects for any changes in volume that occur because of the normalization step e.g. small brains may be stretched to match large brains removing any effect of disease. Intensities within the segmented images are multiplied by the Jacobian values (which essentially are a measure of volume change due to normalization) which means that intensities now represent relative volume.
4) Smoothing – this allows data to be more normally distributed which is required for statistical analysis and reduces the effects of misregistration.
5) Statistical parametric mapping (SPM) – this is the statistical method by which data are examined. Essentially a statistical test (t-test) is performed at each voxel to determine whether there is a statistical difference at that voxel.

In this study VBM was performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm) and the DARTEL toolbox (Ashburner, 2007, Ashburner et al, 2009) with default settings for all parameters. As per the steps described above:

1)/2) Using SPM 5 and the DARTEL toolbox a unified segmentation and spatial normalization procedure is performed. Brain images undergo an initial segmentation process that estimates transformation parameters for warping grey matter (GM), white matter (WM) and cerebrospinal fluid tissue probability maps (TPMs) onto the images. The native space GM and WM segments are then rigidly spatially normalized, using just the rotations and translations from the inverse of the TPM transformation. These "imported" images are then iteratively warped to an evolving estimate of their group-wise GM and WM average template using the DARTEL toolbox. The GM and WM segmentations are then normalized using the final DARTEL transformations.

3) Segmentations are then modulated to account for volume changes.

4) The images are then smoothed using a 6mm full-width at half-maximum (FWHM) Gaussian kernel.

5) An SPM analysis was then performed using a general linear model. The particular model used in each of the studies described in the thesis is shown in the chapter.

Longitudinal volumetric imaging

Rates of atrophy for different brain structures can be calculated by dividing the difference in volume between the repeat and baseline scans by the baseline volume and then adjusting for the time interval between the scans. This requires scans to be registered together (i.e. the scans are aligned so that they are in the same spatial framework). Registration can be linear (i.e. each voxel throughout the image has the same parameters applied) or nonlinear (where the parameters vary throughout the image allowing more accurate registration). In this study, scans were generally initially transformed into standard space by registration to the MNI template (Mazziotta et al, 1995) and then an affine (12 degrees of freedom) registration was performed in order to align the repeat scan onto the baseline image (Woods et al, 1998).

In some cases other methods were used:

Boundary shift integral (BSI)

This is a semi-automated linear registration method which calculates change at the border of the brain (brain/CSF boundary) at every point across a registered pair of scans, summing these to give a value of total volume loss between the two scans (Freeborough et al, 1997b). BSI-derived whole-brain volume changes (BBSI) were expressed as annualized volume change as a percentage of the baseline brain volume.

SIENA

SIENA (Smith et al, 2002) is part of FSL (Smith et al, 2004) and similar to BSI it allows two-timepoint percentage brain volume change to be estimated. The process is similar to BSI: following skull stripping the two scans are aligned (using the skull images to constrain the registration scaling) and segmentation is performed to find the brain/non-brain edge. Perpendicular edge displacement between the two scans is estimated and the mean of these values converted into an estimate of percentage volume loss between the two scans.

Voxel-compression mapping

Linear registration does not allow localization of change between scans. However, non-linear registration techniques can do this by modelling the whole brain. One method is to model the brain as a viscous compressible fluid (Freeborough et al, 1998; Scahill et al, 2002) allowing each voxel to contract or expand to match the other image. The process should lead to a registered repeat image (the second scan) which is an exact match for the baseline image (first scan). The stretch file (Jacobian) gives a value for each voxel which is the extent of contraction or expansion undergone for the second scan to match to the first scan. This stretch file can be seen as a coloured overlay image onto the baseline image (first scan) in order to visualize where the differences are between the scans.

2.2 Neuropsychological methods and techniques

Standard neuropsychological methods and techniques

In the retrospective analyses performed in this study (particularly in chapters 3 and 4) multiple neuropsychological tests are used to examine for the presence of deficits in different cognitive domains:

- Verbal and performance IQ
- Recognition memory (verbal and visual)
- Confrontational naming
- Single word comprehension
- Spelling
- Calculation
- Visuospatial and visuoperceptual skills
- Executive function

The tests used in each part of the study are documented in the particular chapter.

Development of a neurolinguistic battery of tests for use in patients with progressive aphasia

In chapter 5 a battery of neuropsychological tests is used to try to assess various aspects of language in the progressive aphasias and to provide tests that may distinguish between different clinical subtypes.

1) Spontaneous speech

A sample of spontaneous speech was obtained by asking subjects to talk, firstly, freely about their last holiday and, secondly, to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination (Goodglass et al, 1983). Each speech sample was recorded and subsequently transcribed. This allowed for analysis of fluency, the presence of word pauses, the content of the speech (noun and verb frequency) and the presence of agrammatism as well as speech errors and articulatory impairment.

2) Naming

a. All patients were tested on the Graded Naming Test (McKenna et al, 1980), a standardized naming test with control norms. It is a relatively difficult naming test e.g. the first few items are kangaroo, scarecrow and buoy and the last item is retort. This is useful because it can detect subtle naming difficulties and/or changes in performance over time in someone whose premorbid naming capability is well above average.
b. However, as many patients were likely to score near to the floor on the Graded Naming Test, a simple naming test was designed containing 20 items (with the first few items being chair, shoe and pen). All of the pictures were photographs taken from the internet (freely available to download) placed against a white background.

3) Single word comprehension

a. A noun synonyms test (Warrington et al, 1998) e.g. does "javelin" mean the same as "shield" or "spear", was presented visually and aurally
b. A verb synonyms test (Manning et al, 1995) e.g. does "to annihilate" mean "to abandon" or "to destroy", was presented visually and aurally.
c. A word-picture matching test (a shortened version of the British Picture Vocabulary Scale: Dunn et al, 1982) in which patients had to match a word to one of four pictures was presented with the word both written and spoken.

4) Verbal short-term memory, sentence comprehension and grammar

All patients were initially tested on their maximum digit span forwards (with two attempts at each level allowed). Sentence comprehension and verb tense comprehension were subsequently assessed in detail using the following tests:

a. A modified version of the PALPA55 spoken sentence-picture matching (3 alternative forced choice) test (Kay et al, 1992) comprising 24 sentences testing comprehension of reversibility and active/passive constructions.
b. A spoken sentence-picture matching (2 alternative forced choice) test of verb tense comprehension that was an adapted version of the Lesser Syntax test (Lesser, 1974; Parisi et al, 1970) comprising 20 pairs of pictures which differ in whether the agent is doing

something/has done something (present/past comparison, 10 items) or whether the agent is doing something/is about to do something (present/future comparison, 10 items).

5) Speech repetition

Three tests of repetition were performed in all subjects:

a. Sixty single words, consisting of twenty one-syllable, twenty two-syllable and twenty three-syllable words. In each of the sets of twenty words, ten words were of high frequency and ten of low frequency.

1-syllable high frequency	2-syllable high frequency	3-syllable high frequency
wrong	**ready**	**continue**
strike	**nature**	**anything**
song	**minute**	**exercise**
view	**include**	**suddenly**
will	**country**	**together**
sort	**question**	**tomorrow**
cause	**practice**	**different**
stood	**because**	**material**
watch	**against**	**wonderful**
life	**never**	**department**

1-syllable low frequency	2-syllable low frequency	3-syllable low frequency
prowl	**sliver**	**notify**
tout	**robust**	**mutiny**
quirk	**glimmer**	**democracy**
poach	**notion**	**revulsion**
etch	**abstain**	**erratic**
slang	**trample**	**sinister**
gild	**quibble**	**feverish**
hark	**denude**	**cohesion**
mute	**festoon**	**tyranny**
twirl	**collide**	**mutinous**

b. Twenty nonwords consisting of ten three-letter consonant-vowel-consonant words and ten words of 1 to 3-syllables taken from the PALPA8 nonword repetition task (Kay et al, 1992).

mip

lub

dak

pel

rop

nuv

bim

pab

fep

vot

splack

cleast

prench

grank

gaffic

larden

polid

ality

enitor

inima

c. twenty sentences (McCarthy et al, 1984), consisting of A) ten sentence clichés e.g. "As blind as a bat", "A flash in the pan", and B) ten novel sentences e.g. "She met me at the airport", "He mended the plug". Sentence length varied between 3 and 7 words without a significant difference in length between the clichés (4.4 words per sentence) and novel sentences (4.8 words per sentence).

6) Reading and spelling

Patients were tested on three reading tests:

a. The Schonell Reading Test (Schonell et al, 1952), a mixture of different types of words (score out of 100)

b. An irregular word reading test (score out of 30) was designed to look for the presence of surface dyslexia i.e. regularization of irregular words on reading.

Examples:

touch

plumb

aisle

subtle

c. The Graded Difficulty Nonword Reading Test (Snowling et al, 1996; score out of 20).

Examples:

hast

kisp

mosp

drant

Patients were also tested on the Graded Difficulty Spelling Test (Baxter et al, 1994), a series of 30 graded difficulty words, starting with two, world, said and ending with cemetery, kaleidoscope, and iridescent.

3. Neuroanatomy of language impairment in FTLD

There are a number of studies that have previously looked at various aspects of neuroimaging in PNFA and SD (reviewed in 3.1) but the studies in this chapter were designed to look at novel ways of examining the patterns of cell loss in PNFA and SD, using a large cohort of patients that includes a subgroup with pathologically-confirmed FTLD (3.2). Initially, the relatively new method of looking at the thickness of the cortex using automated software was used to examine the neuroimaging patterns in PNFA and SD, including how cortical thickness changes with disease severity (3.3). There have been few longitudinal studies of PNFA or SD and the last part of this Chapter describes a study using volumetric imaging measures to identify patterns of change over time (3.4).

The specific hypotheses of Chapter 3 are:

1. Patterns of cortical thinning in PNFA and SD will overlap substantially with the patterns seen in other imaging techniques.
2. Patterns of cortical thinning in the whole clinical cohort will be similar to those seen in the smaller pathological cohort.
3. Rates of whole brain atrophy will be similar in PNFA and SD and greater than controls.
4. Rates of atrophy in regions of interest will differ between the two hemispheres in PNFA and SD.
5. Patterns of change in the regions of interest over time will map onto known changes in the clinical syndrome. In particular increasing right temporal lobe involvement will be seen in SD consistent with increasing behavioural symptoms.

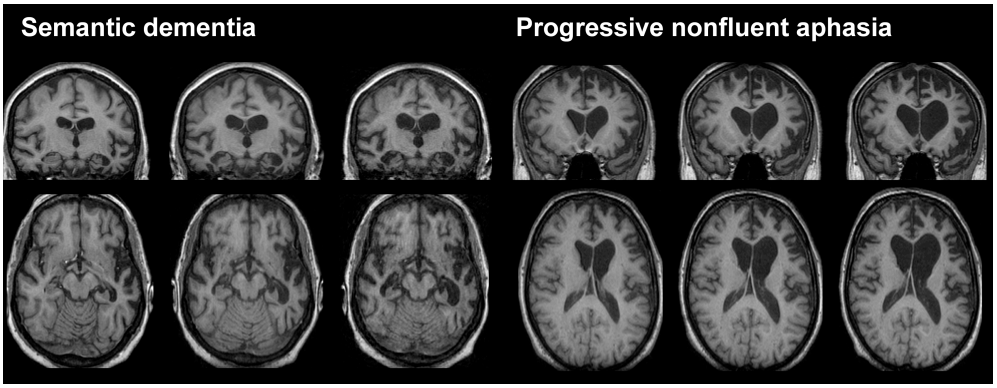
3.1 Overview of previous neuroimaging studies

The most common type of imaging of PNFA and SD has been cross-sectional structural magnetic resonance imaging (MRI) or functional imaging (positron emission tomography, PET, or single photon emission computed tomography, SPECT) studies of patterns of atrophy or hypometabolism. The majority of these studies have used whole brain or voxel-wise imaging methods such as statistical parametric mapping (SPM) but some have also looked at particular regions of interest such as specific temporal lobe structures.

Atrophy or hypometabolism in PNFA and SD is usually asymmetrical, being worse in the left hemisphere, with structural and functional imaging studies showing similar findings (Desgranges et al, 2007; Panegyres et al, 2008). However, there are also left-handed patients described with greater right hemisphere involvement (Drzezga et al, 2002; Mesulam et al, 2005). Examples of longitudinal series of structural images in patients with pathologically-confirmed SD (TDP-43 positive type 1, Sampathu classification) and PNFA (tau-positive Pick's disease) are shown in Figure 3.1.1.

Figure 3.1.1

Longitudinal series of coronal and axial T1 MR images from pathologically-confirmed patients with SD (TDP-43-positive pathology type 1, Sampathu classification) and PNFA (tau-positive Pick's disease). Three scans, registered into the same space and each separated by approximately one year, are shown in order to highlight the progression in atrophy, as described in the summary section. The images are shown in radiological convention i.e. left hemisphere on the right of the picture.



SD is the most comprehensively studied in terms of cross-sectional patterns of atrophy (Mummery et al, 1999; Mummery et al, 2000; Chan et al, 2001b; Galton et al, 2001: Rosen et al, 2002a; Boxer et al, 2003; Grossman et al, 2004; Halpern et al, 2004; Studholme et al, 2004; Davies et al, 2004; Gorno-Tempini et al, 2004a; Gold et al, 2005; Short et al, 2005; Schroeter et al, 2007; Lindberg et al, 2009; Pereira et al, 2009). Initial VBM studies of clinically diagnosed SD identified an asymmetrical pattern of atrophy affecting mainly the anterior, inferior and lateral temporal lobes, more so in the left hemisphere (Mummery et al, 1999; Mummery et al, 2000). The findings of these studies were extended by detailed region of interest (ROI) studies of temporal lobe structures which showed that the temporal pole, fusiform gyrus, entorhinal cortex, inferior temporal gyrus as well as the amygdala and hippocampus were the most affected areas with relative sparing of the superior temporal gyrus; there was also the presence of an antero-posterior gradient with relatively less atrophy posteriorly (Chan et al, 2001b; Galton et al, 2001). Further VBM studies showed that there may be involvement of areas outside the temporal lobes in SD, particularly orbitofrontal, insular and anterior cingulate cortices (Rosen et al, 2002a). This asymmetrical temporal, frontal and anterior cingulate pattern distinguishes SD from Alzheimer's disease (AD), which has more symmetrical hippocampal atrophy involvement without an antero-posterior gradient (Chan et al, 2001b) and greater posterior cingulate and parietal lobe atrophy (Boxer et al, 2003). ROI and VBM studies have been shown to produce similar results (using either manual segmentation e.g. Chan et al, 2001b; Good et al, 2002, or a visual rating scale e.g. van de Pol et al, 2006; Davies et al, 2009). A small VBM study of pathologically-confirmed patients found that patterns of atrophy were similar in SD cases associated with both ubiquitin-positive and tau-positive FTLD pathology but in the rare cases with Alzheimer's pathology there was mainly left hippocampal atrophy (Pereira et al, 2009). Similar patterns of asymmetrical temporal lobe hypometabolism have been found in PET and SPECT imaging (Soriani-Lefevre et al, 2003; Diehl et al, 2004; Clark et al, 2005; Drzezga et al, 2008). There have been a couple of studies of white matter disease in SD (Chao et al, 2007; Borroni et al, 2007) with one diffusion tensor imaging (DTI) study showing particular involvement of the inferior longitudinal fasciculus with additional

involvement of inferior fronto-occipital fasciculus, callosal and superior longitudinal fasciculus tracts (Borroni et al, 2007).

The majority of SD cases described in the literature have asymmetrical left greater than right temporal lobe atrophy but there are a number of reports of the opposite pattern with right greater than left temporal lobe atrophy (Rosen et al, 2002b; Thompson et al, 2003; Gorno-Tempini et al, 2004c; Seeley et al, 2005; Chan et al, 2009). This right temporal variant appears to be less common than the left temporal variant although this may simply represent an ascertainment bias. Patients often have initial behavioural symptoms rather than a progressive aphasia (Seeley et al, 2005) with the development of semantic impairment only later in the illness (leading some authors to argue that this right temporal variant should be logically separated from the primary progressive aphasias e.g. Mesulam et al, 2009). The pattern of atrophy in these right temporal variant appears to be the mirror image of the left temporal variant (Brambati et al, 2009b), although the underlying pathology remains unclear.

Longitudinal studies in SD are less common (Chan et al, 2001a; Whitwell et al, 2004; Diehl-Schmid et al, 2006; Bright et al, 2008; Czarnecki et al, 2008; Brambati et al, 2009b; Knopman et al, 2009; Krueger et al, 2009). In those with the left temporal variant there seems to be increased right temporal lobe involvement as the disease progresses as well as spread of atrophy within the left hemisphere, particularly more posterior temporal areas and the orbitofrontal, anterior insular, inferior frontal and anterior cingulate lobes (Diehl-Schmid et al, 2006; Bright et al, 2008; Brambati et al, 2009b). In the right temporal variant, limited evidence suggests that a similar but mirror-image pattern of atrophy spread is seen (Brambati et al, 2009b).

PNFA is less well-studied than SD and patterns of neuroanatomical involvement are not quite so clear (Nestor et al, 2003; Gorno-Tempini et al, 2004a; Grossman et al, 2004; Zahn et al, 2005; Josephs et al, 2006; Ogar et al, 2007; Schroeter et al, 2007; Nestor et al, 2007; Lindberg et al, 2009). This is partly because of the heterogeneity of PNFA and also the differences in

definition between research groups. Similar to SD, atrophy or hypometabolism is usually asymmetrical and more marked in the left hemisphere. The most significantly affected areas are in the left inferior frontal lobe (particularly the frontal opercular region) and anterior insula (Nestor et al, 2003; Gorno-Tempini et al, 2004a; Ogar et al, 2007). However, left middle and superior frontal, superior temporal and caudate involvement are also frequently reported in studies with less frequent involvement of anterior parietal lobes (Gorno-Tempini et al, 2004a; Ogar et al, 2007). ROI studies are limited in PNFA (van de Pol et al, 2006; Looi et al, 2008; Chow et al, 2008; Looi et al, 2009) but have shown involvement of striatal structures, particularly the caudate. There are few pathologically-confirmed studies of PNFA and these have often studied mixed pathological groups but despite this have shown fairly consistent findings compared to the clinical studies e.g. anterior insula and inferior frontal involvement in mixed groups of tau-positive patients (Josephs et al, 2006).

There are limited longitudinal studies of PNFA (Gorno-Tempini et al, 2004b), although it seems that with disease progression there is spread from the left inferior frontal and insular cortex to involve superior temporal, middle and superior frontal and anterior parietal lobes (Gorno-Tempini et al, 2004b). More posterior atrophy, particularly of the left anterior parietal lobe, may herald the presence of an accompanying corticobasal syndrome (CBS) (Gorno-Tempini et al, 2004b).

3.2 Methods

Patient cohort

The patients included in the studies in this chapter were those with a clinical diagnosis of PNFA or SD according to consensus criteria who had attended the National Hospital for Neurology and Neurosurgery Specialist Cognitive Disorders Clinic, Queen Square, London and who had had at least one volumetric 1.5T MRI brain scan. Patients were identified by performing a retrospective review of the Specialist Cognitive Disorders Clinic patient database. For SD the criteria used were modified Neary criteria as per Adlam et al, 2006 (Neary et al, 1998; Adlam et al, 2006) whilst for PNFA diagnosis was based on Neary criteria (Neary et al, 1998) with patients having a speech production impairment characterized by agrammatism and apraxia of speech. These criteria allow patients with SD and PNFA to be separated on clinical or neuropsychological grounds, independent of imaging findings.

For the cross-sectional study (3.3) there were 44 SD patients and 32 PNFA patients. A control group of 29 cognitively-normal subjects matched for gender and age was also studied for comparison. There were no significant differences between any of the groups in terms of gender, age or duration at scan (Table 3.2.1).

Table 3.2.1

Demographic data for the SD, PNFA and control groups in the cross-sectional study i.e. who had had at least one volumetric MRI scan. Age and duration at scan are mean values in years with standard deviation in parentheses.

Group	Number	% male	Age at scan (years)	Duration at scan (years)
SD	44	59	64.1 (7.5)	4.3 (1.8)
PNFA	32	66	65.8 (7.7)	4.4 (2.0)
Controls	29	60	65.2 (8.7)	N/A

Eleven SD patients were known to be pathologically-confirmed at the time of study: 64% male, mean age at scan 65.9 (5.9) years old, mean duration 4.7 (2.5) years, with type 1 FTLD-TDP pathology in all cases (Cairns et al, 2007). Four PNFA patients were pathologically-confirmed: 75% male, mean age at scan 62.7 (7.0) years old, mean duration 4.4 (0.6) years, with tau-positive pathology in all cases (two patients had corticobasal degeneration and two had Pick's disease).

For the longitudinal study, all patients with two or more scans were included: there were 21 patients with SD (8 with pathological-confirmation, all with type 1 FTLD-TDP) and 24 patients with PNFA (2 with pathological-confirmation, one with Pick's disease and one with corticobasal degeneration). A control group of 20 cognitively-normal subjects was also included for comparison. There were no significant differences in age, gender, or interscan interval between any of the groups.

Table 3.2.2

Demographic data for the SD, PNFA and control groups in the longitudinal study i.e. who had had at least two volumetric MRI scans. Age and duration at scan as well as interscan interval for the first two scans are mean values in years with standard deviation in parentheses.

Group	Number	% male	Age at scan (years)	Duration at scan (years)	Interscan interval (years)
SD	21	57	64.2 (7.2)	3.9 (1.5)	1.5 (0.9)
PNFA	24	63	66.6 (6.6)	5.2 (2.1)	1.3 (0.6)
Controls	20	60	63.8 (9.1)	N/A	1.7 (0.9)

3.3 Patterns of cortical thinning in PNFA and SD

The measurement of cortical thickness can provide complementary information to other imaging techniques about the neuroanatomy of neurodegenerative disorders as it allows the regional distribution and quantification of grey matter cortical loss to be specifically assessed in contrast to gyral or lobar volumetric studies which combine grey and white matter within regional volumes. There are currently few studies that have examined cortical thinning in neurodegenerative disease (Gold et al, 2005; Lerch et al, 2005; Dickerson et al, 2007; Rosas et al, 2008) and so the objective of this study was to look at the cross-sectional patterns of cortical thickness in PNFA and SD.

METHODS

Cortical reconstruction and thickness estimation was performed as described in Chapter 2. A vertex-by-vertex analysis using a general linear model was performed to examine differences in cortical thickness between the patient groups and the control group. Cortical thickness, C, was modelled as a function of group, controlling for age, sex and the scanner used by including them as nuisance covariates. $C=\beta_1$ SD + β_2 PNFA + β_3 controls + β_4 age + β_5 sex + β_6 scanner + $\mu + \varepsilon$ (where μ is a constant, and ε is error) with the contrasts of interest being the two-tailed t-tests between the estimates of the group parameters, i.e. β_1 and β_3, β_2 and β_3. Maps showing the significant differences between the disease groups and controls were generated, correcting for multiple comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.05 significance level.

In order to examine changes in cortical thickness as the disease progressed performance on naming tests was used as a measure of disease severity. Other markers of disease severity such as estimated disease duration may be unreliable and subject to recall bias, while global indices of cognitive function such as the MMSE (Folstein et al, 1975) are insensitive and may not be relevant to the specific deficits produced by the language-based dementias. In contrast, impaired naming ability is observed in both language variants of FTLD and central to the clinical syndrome in each case, and performance can be easily quantified: naming

performance is therefore a suitable index of clinical severity that can be applied across individuals and groups. The standard naming test performed in patients who attend the Specialist Cognitive Disorders Clinic is the Graded Naming Test (GNT) (McKenna et al, 1980) but this is a difficult naming test and when patients become very anomic and unable to score on this test (e.g. in patients with moderate to severe SD) the easier Oldfield Naming Test (Oldfield et al, 1965) is usually performed. In order to compare scores between these two tests a group of 55 patients with a neurodegenerative disease and 55 cognitively-normal controls have previously performed both tests and a conversion table generated allowing an equivalent score to be calculated. 28 patients with SD and 28 patients with PNFA performed one of the two naming tests within six months of the time of the scan and were therefore used for the analysis: mean equivalent Oldfield score in the SD group was 6.2 (standard deviation 4.8) and in the PNFA group was 21.4 (6.7). In both groups the patients were divided into three groups based on their naming scores. In PNFA group 1 (the least anomic) were those who could score within the normal range i.e. above the 5th percentile (greater than 13 on the GNT or an equivalent score of greater than 24 on the Oldfield Naming Test) and group 3 (the most anomic) were those unable to score on the Graded Naming Test or worse (equivalent to less than 14 on the Oldfield Naming Test) with group 2 those scoring in between these values (Table 3.3.1). Patients with SD scored lower as a group than PNFA with all scoring below the 1st percentile and were therefore split into three approximately equal-numbered groups allowing for some patients scoring equally (Table 3.3.1). Effect size maps were generated based on the difference in mean thickness in each of these severity subgroups and in the whole SD and PNFA groups, comparing each to the controls and expressing the disease-control difference as a percentage of the mean control group thickness. As well as the surface maps, the Freesurfer processing stream also generates thickness measures from 33 cortical regions of interest as described in Desikan et al, 2006. Mean cortical thickness was calculated from these regions to create a mean lobar thickness and there are shown for each lobe in the different severity groups in Table 3.3.1.

RESULTS

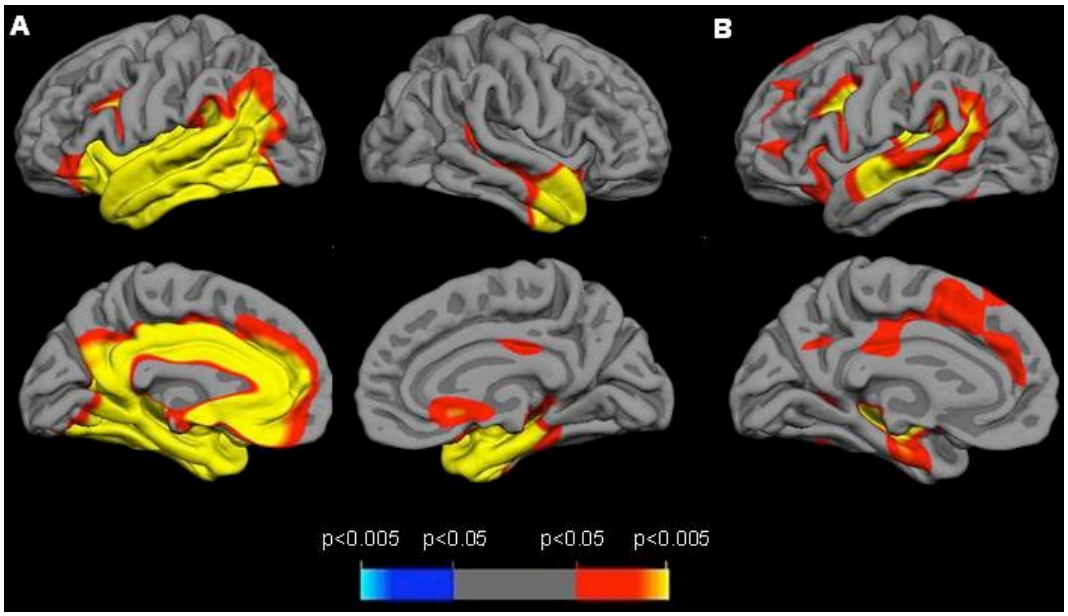
Whole group analysis (Figure 3.3.1)

Compared with the healthy control group, in the SD group there was thinning of the cortex in an asymmetric pattern, most prominently affecting the temporal lobes on the left more than the right (Figure 3.3.1A). The areas of greatest thinning were anterior and inferior in the temporal lobes: on the left, the most affected areas were the temporal pole (reduced by 51% relative to control mean thickness), entorhinal cortex (46%), parahippocampal (30%), fusiform (27%) and inferior temporal (26%) gyri. On the right a similar but less extensive pattern of thinning was seen, particularly affecting the entorhinal cortex (reduced by 25% relative to control mean thickness), temporal pole (19%) and parahippocampal (14%) areas. Areas outside the temporal cortices were also affected although to a lesser extent; in particular thinning was seen in the left orbitofrontal, insular, inferior frontal and (particularly anterior) cingulate cortices (Figure 3.3.1A).

In the PNFA group the most significant areas of thinning were in the superior areas of the left temporal lobe (banks of the superior temporal sulcus (reduced by 14% relative to control mean thickness), superior temporal lobe (10%) and transverse temporal gyrus (9%)) as well as both left inferior frontal (pars opercularis, 9% and triangularis, 9%) and superior frontal lobes (9%) (Figure 3.3.1B). Cortical thinning was also seen in the left insula (although there is no region of interest cortical label for this area in Freesurfer and therefore no measure of the extent of thinning). There were no significant areas of thinning in the right hemisphere.

Figure 3.3.1

Pattern of significantly thinner cortex in A) SD and B) PNFA compared with controls (coloured bar represents FDR corrected p-values)



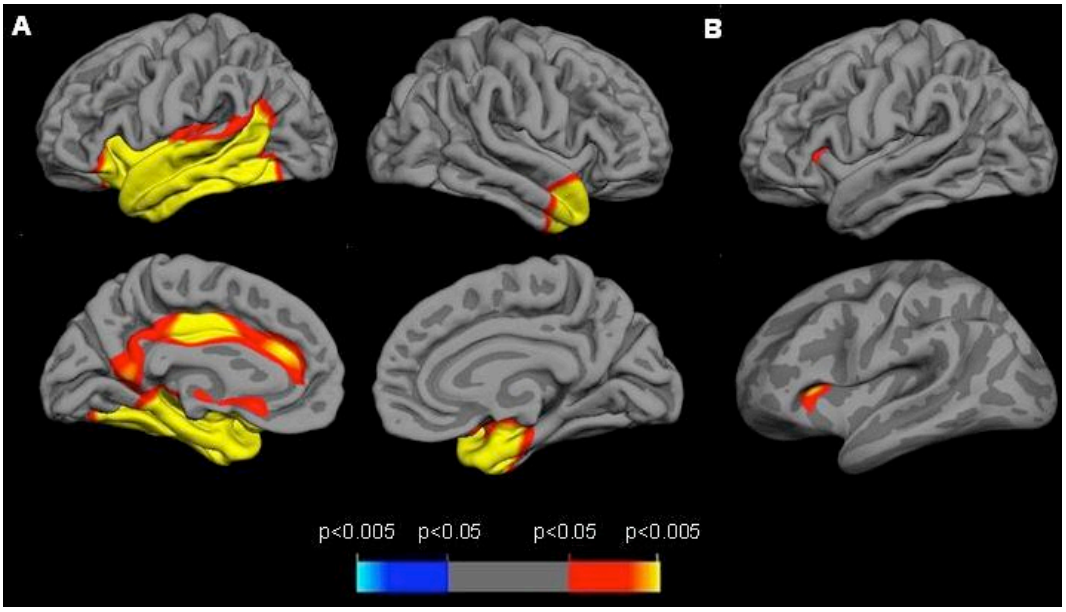
Pathologically-confirmed subgroup analysis (Figure 3.3.2)

A similar pattern of cortical thinning was seen in the pathologically-confirmed SD group compared with the whole SD group (Figure 3.3.2A) with asymmetric left greater than right thinning of the temporal lobe cortices.

The smaller pathologically-confirmed PNFA group showed only one area of significant thinning in the left insula (Figure 3.3.2B, top), which is seen more clearly on the inflated cortical map (Figure 3.3.2B, bottom).

Figure 3.3.2

Pattern of significantly thinner cortex in A) pathologically-confirmed SD and B) pathologically-confirmed PNFA (represented on an averaged brain, top, and an inflated cortical map, bottom) compared with controls (coloured bar represents FDR corrected p-values)



Modelling severity using performance on naming task (Figures 3.3.3 and 3.3.4)

In SD there was greater thinning of the temporal lobe cortices as the disease became more severe (as assessed by the severity of anomia) (Table 3.3.1). In the least affected group the predominant thinning was in the anterior and inferior parts of the left temporal lobe with a similar but less affected area in the right temporal lobe (Figure 3.3.3). As the disease became more severe, there was involvement of more posterior and superior parts of the left temporal lobe, parts of the left frontal lobe (orbitofrontal and inferior gyri) and the insula and cingulate gyrus. A similar pattern of evolution with increasing disease severity was observed in the right temporal lobe cortex.

In PNFA there was also greater thinning of the cortices as the disease became more severe (Table 3.3.1). In the least affected group the areas of thinning were in the left inferior frontal gyrus, insula and areas of the superior temporal lobe. As the disease became more severe,

these areas became thinner and there was additional involvement of the lateral left temporal lobe, anterior parietal lobe and middle and superior parts of the frontal lobe (Figure 3.3.4).

Figure 3.3.3

Percentage cortical thickness difference from controls in SD in groups 1, 2, 3 and the total group (only lateral views are shown, coloured bar represents percentage thickness difference).

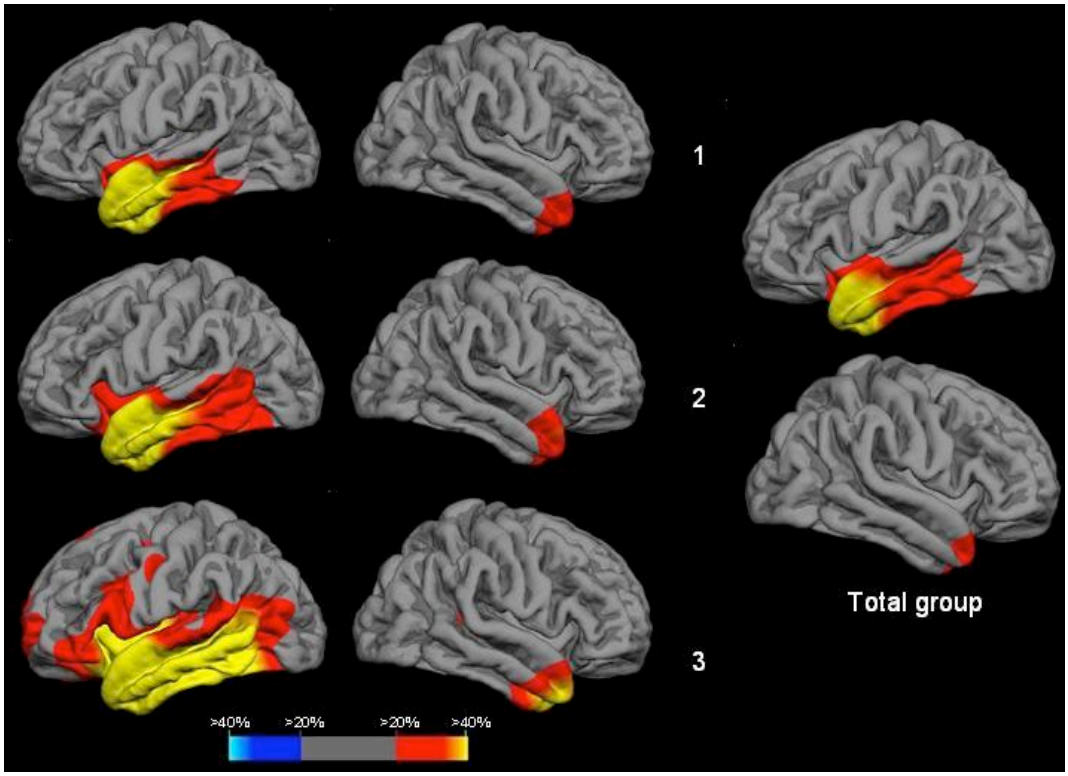


Figure 3.3.4

Percentage cortical thickness difference from controls in PNFA in groups 1, 2, 3 and the total group (only lateral views are shown, coloured bar represents percentage thickness difference).

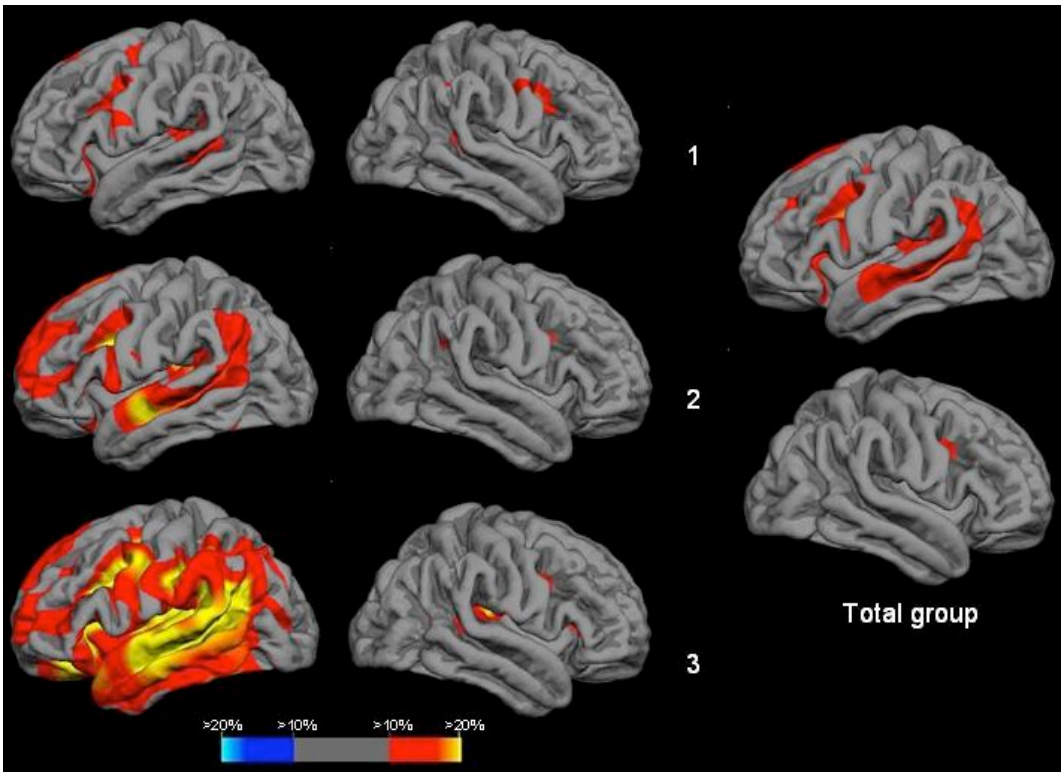


Table 3.3.1

Comparison of disease groups by naming score (equivalent Oldfield score) and cortical thickness in each lobe (*p<0.05 disease group versus controls, N = number of patients)

Group	N	Range of naming scores	Mean (standard deviation) naming score	Mean (standard deviation) cortical thickness in each lobe (mm)					
				Frontal		Temporal		Parietal	
				Left	Right	Left	Right	Left	Right
SD 1	9	>9	12.0 (2.0)	2.1 (0.2)	2.2 (0.1)	1.7 (0.2)*	2.1 (0.2)*	2.0 (0.1)	2.0 (0.2)
SD 2	11	3-9	5.4 (2.0)	2.0 (0.1)	2.1 (0.2)	1.6 (0.1)*	2.0 (0.2)*	1.8 (0.1)	1.9 (0.2)
SD 3	8	<3	0.8 (0.9)	1.8 (0.1)*	2.1 (0.2)	1.5 (0.1)*	2.0 (0.1)*	1.7 (0.1)*	1.9 (0.2)
PNFA 1	11	>24	26.8 (1.0)	2.1 (0.2)	2.1 (0.2)	2.3 (0.3)	2.3 (0.4)	1.9 (0.2)	1.9 (0.2)
PNFA 2	11	14-24	19.7 (4.1)	2.0 (0.1)	2.2 (0.2)	2.2 (0.3)	2.4 (0.3)	1.9 (0.1)	2.0 (0.2)
PNFA 3	6	<14	10.5 (3.0)	2.0 (0.1)*	2.1 (0.1)	2.0 (0.3)*	2.3 (0.4)	1.8 (0.1)*	1.9 (0.2)
Controls	29	N/A	N/A	2.2 (0.2)	2.2 (0.1)	2.4 (0.3)	2.3 (0.3)	2.0 (0.2)	2.0 (0.2)

DISCUSSION

This study shows that there are distinct patterns of cortical thinning in SD and PNFA. The findings of predominantly asymmetric left greater than right temporal lobe atrophy in SD and predominantly left-sided superior temporal, inferior frontal lobe and insular atrophy in PNFA are consistent with previous reports using other image analysis techniques described in Chapter 3.1. These findings further suggest that increasing disease severity is associated with distinct patterns of evolution of cortical thinning beyond these core regions: into the left frontal, insular and cingulate cortices in SD, and into left middle and superior frontal lobe and anterior left parietal lobe in PNFA.

The initial and canonical feature of SD is progressive degradation of semantic knowledge resulting in anomia and impaired single word comprehension. Theories of semantic memory localization suggest the anterior left temporal lobe plays a critical role and this would be

consistent with the early involvement of this core area even in the least affected SD group. In PNFA the initial clinical feature is often apraxia of speech, which has been associated with left insula involvement (Dronkers, 1996; Ogar et al, 2007) and agrammatism, which has been associated with left inferior frontal lobe damage (Amici et al, 2007). Other regions of superior temporal cortex involved in the PNFA group here, in particular the superior temporal sulcus and transverse temporal gyrus, mediate the analysis, transcoding and short term storage of speech signals (Scott et al, 2003). Damage involving these areas might contribute to impairments of phonological encoding, working memory and grammar processing that are often prominent in this group suggesting testable hypotheses for future work. In the pathologically-confirmed subgroup of PNFA patients the most significant area of thinning was in the insular cortex consistent with previous findings that this area is critical for the development of speech production deficits in PNFA (Nestor et al, 2003).

The findings concerning the effects of disease severity on cortical thinning in SD and PNFA are based on the analysis of stratified cross-sectional data indexed using a key neuropsychological function (naming performance), rather than longitudinal measurements in individual patients. However, allowing this caveat, the stratified cross-sectional findings are consistent with available data on patterns of disease evolution in SD and PNFA. In SD, disease progression is associated with the development of impairments of behaviour and social cognition (Rosen et al, 2006) and symptoms attributable to right temporal lobe dysfunction such as prosopagnosia (Seeley et al, 2005). These clinical features are consistent with the thinning of frontal (particularly left orbitofrontal), insula, right temporal and posterior temporal cortices observed in the more severely affected SD group here. In PNFA, disease progression is associated with increasing difficulties with speech repetition and often the emergence of non-language symptoms such as limb apraxia and dyscalculia, consistent with spread through the temporal lobes posteriorly to involve the left parietal lobe. There are few longitudinal imaging studies of either SD or PNFA (Whitwell et al, 2004; Bright et al, 2008; Brambati et al, 2009b). Although other studies have generally used estimated disease duration as a surrogate of severity, the patterns of disease spread described previously are qualitatively similar to those observed here:

namely, increasing involvement of right temporal and posterior temporal and left inferior frontal areas in SD, and more dorsal posterior left temporal and parietal areas in PNFA. However, the data concerning PNFA in particular should be interpreted with caution, given that pathological confirmation was available in only a minority of cases. The PNFA syndrome is likely to be pathologically heterogeneous, and involvement of parietal and other posterior cortical areas may be produced by specific pathological substrates rather than as a consequence of disease evolution per se. Resolution of this issue must await more complete histopathological data for the PNFA group.

Measures of cortical thickness have been performed in various neurodegenerative diseases using a number of different techniques. From the neurobiological perspective, this technique can potentially provide important complementary information about cortical areas (such as the superior temporal sulcus region) that are likely to be crucial in the pathophysiology of the language-based dementias but difficult to assess using conventional imaging modalities on anatomical or geometrical grounds. The clinical utility of cortical thickness measurement has not been widely evaluated. Furthermore, the various techniques currently in use have not yet been adequately compared (Fischl et al, 2000; Kim et al, 2005; Hutton et al, 2008). Evaluation of the sensitivity and specificity of cortical thickness techniques, hypothesis-driven correlation with behavioural, pathological and other neuroimaging data, and longitudinal studies in degenerative disease are clear directions for future work.

3.4 Longitudinal volumetric imaging and sample sizes in PNFA and SD

There are currently few longitudinal imaging studies of PNFA and SD and hence little is known about the patterns of change in cell loss over time (Whitwell et al, 2004; Bright et al, 2008; Brambati et al, 2009b). Information about such change will be important not only to understand these diseases more clearly but also because of the need to develop useful biomarkers of disease progression for clinical trials (Fox et al, 2005). This study was therefore designed with two aims: to characterise profiles of whole-brain and hemispheric atrophy longitudinally in PNFA and SD as well as temporal lobe atrophy in SD, and to determine whether such measures could constitute feasible imaging biomarkers for therapeutic trials in PNFA and SD.

METHODS

Image analysis was performed using the MIDAS software package (Freeborough et al, 1997a). Volumetric analysis was performed as described in Chapter 2. Segmentation was performed blinded to the subject's identity, whether in the disease or control group, whether measurements were being performed on the baseline or registered-repeat image, and the left–right orientation of the scan.

Statistics and sample size calculations

The two disease groups and the healthy control group were compared statistically based on contrasts between the group means using a linear regression model in STATA 10 (Stata Corporation, College Station, TX). 95% bias-corrected bootstrap confidence intervals with 1000 replicates were used. Standard methods were used to calculate sample sizes for detection of a moderate treatment effect (30% reduction in atrophy adjusting for control atrophy rate), including baseline and one follow-up assessment with 90% power and 5% two-tailed significance level (Fox et al, 2000).

RESULTS

Whole brain, hemisphere and ventricle volumetric measurement in PNFA and SD

Baseline brain and hemisphere volumes were smaller in the PNFA and SD groups compared to controls with ventricle volumes being larger in the disease groups. Left/right hemispheric asymmetry ratios in PNFA and SD were significantly lower than control ratios at baseline but not significantly different between the disease groups (Table 3.4.1).

Table 3.4.1

Baseline volumetric MRI data for the control, SD and PNFA groups

	Controls	SD	PNFA
Baseline brain volume (ml)	1180.6 (96.8)	1110.1 (106.6)	1054.5 (137.6)
Baseline left hemisphere volume (ml)	581.4 (45.4)	528.7(46.5)	513.6 (60.2)
Baseline right hemisphere volume (ml)	579.5 (47.8)	561.9 (56.1)	537.8 (64.0)
Baseline left/right hemisphere ratio	1.00 (0.01)	0.94 (0.03)	0.96 (0.04)
Baseline ventricular volume (ml)	27.7 (23.8)	43.1 (19.7)	43.7 (19.4)

Rates of whole brain atrophy and ventricular enlargement were greater in each of the disease groups compared with controls with no significant differences between the disease groups (Tables 3.4.2). As in previous studies comparing BSI and SIENA, the SIENA rates were slightly higher than those found using BSI (Smith et al, 2007). Left hemisphere rates of atrophy were significantly greater than right hemisphere rates within disease groups however there were no significant differences in rates of left or right hemisphere atrophy between PNFA and SD (Tables 3.4.2). Hemispheric asymmetry (left/right hemisphere ratio) significantly increased in the SD groups over time with a non-significant trend toward increasing in the total PNFA group (Tables 3.4.2). However, three PNFA patients started with right greater than left asymmetry (two of whom were known to be left-handed) and if these patients were excluded from the analysis there was a significant increase in the left/right hemispheric asymmetry in the PNFA group.

Table 3.4.2

Rates of whole brain atrophy, ventricular enlargement, hemispheric atrophy and change in left/right hemisphere ratio ([1] Enlargement rate for ventricle BSI, * p<0.05, disease group worse than controls).

Outcome measure	Mean rate of atrophy[1] (standard deviation)		
	Controls	SD	PNFA
Brain BSI (%/yr)	0.3 (0.4)	2.5 (1.5)*	2.5 (1.1)*
Brain SIENA (%/yr)	0.5 (0.3)	3.2 (1.3)*	3.4 (1.7)*
Left hemisphere rate (%/yr)	0.3 (0.9)	3.6 (3.0)*	4.2 (1.8)*
Right hemisphere rate (%/yr)	0.0 (0.9)	2.8 (2.8)*	3.4 (1.9)*
L/R hemisphere ratio change (%/yr)	0.3 (0.7)	0.8 (1.0)*	0.8 (1.1)
Ventricle BSI (ml/yr)	0.7 (1.0)	6.9 (3.8)*	6.5 (3.4)*

Sample size calculation

Estimated sample sizes (Table 3.4.3) were smallest for left hemisphere rate and whole brain BSI in the PNFA group and for whole brain SIENA measurement in the SD group.

Table 3.4.3

Sample size required per treatment arm using different measurement methods, based on 90% power to detect a difference ([1] Enlargement rate for ventricle BSI).

	Sample size per treatment arm (30% reduction in atrophy rate[1])	
	SD	PNFA
Brain BSI	109	59
Brain SIENA	63	81
Ventricle BSI	88	81
Left hemisphere rate	193	50
Right hemisphere rate	234	73

Temporal lobe volumetric measurement in SD

The mean (standard deviation) baseline left temporal lobe volume was 31.9ml (6.9ml) in the SD group and 61.3ml (5.8ml) in the controls, whereas the mean baseline right temporal lobe volume was 49.2ml (9.5ml) in the SD group and 64.8ml (6.8ml) in the controls. The mean baseline left temporal lobe volume was significantly smaller than the right in the SD group. The mean annualized rates of both left and right temporal lobe atrophy were significantly greater in the SD group compared with controls (Table 3.4.4). However, the right temporal lobe atrophy rate for the SD group was significantly greater than the left temporal lobe atrophy rate (p=0.02). Furthermore, right and left temporal lobe atrophy rates were correlated, R^2 = 0.31, p=0.008 (Figure 3.4.1). The data from the subgroup of eight patients who had pathological confirmation of disease were also analyzed with no evidence for differences between the pathologically-confirmed and the non-pathologically-confirmed SD groups.

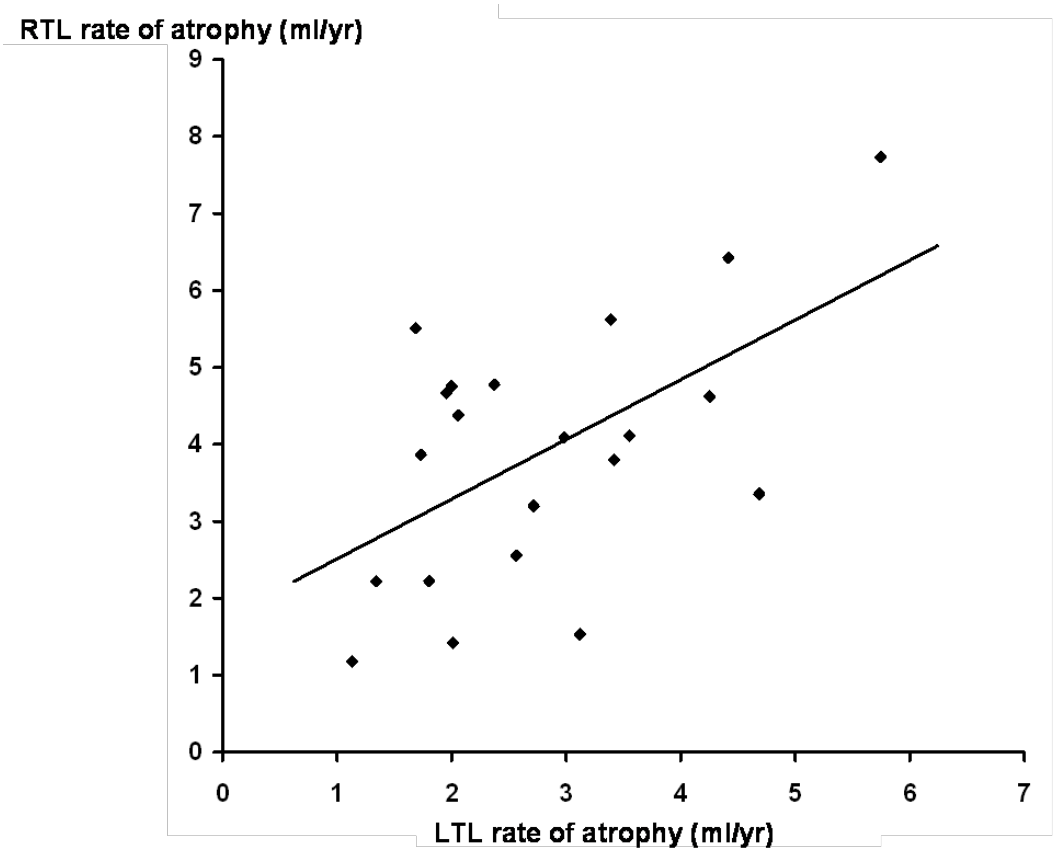
Table 3.4.4

Annualized rates of temporal lobe atrophy in the control group, total SD group and pathologically-confirmed SD group

	Mean rate of atrophy (standard deviation) ml/year		
	Controls	**Total SD**	**Path-confirmed SD**
Left temporal lobe	0.4 (0.6)	2.8 (1.2)	2.5 (1.0)
Right temporal lobe	0.4 (0.8)	3.9 (1.7)	4.0 (1.2)

Figure 3.4.1

Rate of atrophy of the right temporal lobe as a function of the rate of atrophy of the left temporal lobe in each of the 21 patients with semantic dementia



Sample size calculations revealed a number per treatment arm of 60 for the left temporal lobe and 55 for the right temporal lobe i.e. substantially smaller than if whole brain or hemisphere volumes were used.

DISCUSSION

This study provides profiles of longitudinal global and regional brain atrophy in a cohort of patients with SD and PNFA. Both groups have asymmetrical (predominantly left-sided) cerebral atrophy at baseline with increasing asymmetry as the disease progresses. Overall rates of progression (based on whole brain or hemispheric atrophy rates) were similar between the groups.

The basis for increasing cerebral asymmetry with disease evolution in SD and PNFA is an unresolved issue with neurobiological implications. This longitudinal change in hemispheric ratio is not attributable simply to an arithmetical effect, which would follow if both hemispheres atrophied at a similar fixed rate: rather, the increase in hemispheric asymmetry was underpinned by a genuine disproportionate increase in left hemisphere atrophy. On face value this finding appears to run counter to the widely held view that focal dementias become 'global' brain diseases over time, with more or less uniform involvement as an endpoint. To address this issue will require detailed regional analysis of the profile of longitudinal changes within as well as between hemispheres, as well as systematic sampling of atrophy rates throughout the course of the disease. One interpretation is that, at least during the phase of mid-stage disease, atrophy spread occurs via a mainly intrahemispheric network of connected brain regions, tending to 'focus' the effects of the pathological process within the more damaged (left) hemisphere. This interpretation would be consonant with other emerging evidence of network-specific damage in FTLD syndromes (Seeley et al, 2009) and suggests testable hypotheses about the mechanism of brain damage in FTLD more generally.

The sample size calculations in this study have implications for the design of future trials of disease-modifying therapy in SD and PNFA (Knopman et al, 2008; Knopman et al, 2009). For SD, smaller sample sizes may be needed in clinical trials if MR measures of particular regions of interest (temporal lobes) are used rather than measures of whole brain, hemisphere or ventricular volume change. Measures of rate of atrophy for the left hemisphere in PNFA would yield practically useful sample sizes, however (by analogy with SD) the use of more specific regions of interest (e.g. inferior frontal lobe or insula) might improve sample size estimates. One further caveat is that this study used manual segmentation of the temporal lobes. Although this has good intra-rater reliability, it is relatively time-consuming and requires training of the segmentor. Development of more automated measurements would be useful and there are a number of possible approaches (e.g. template-based segmentation of temporal lobes) – these would need to be validated in SD scans but if reliable they may be easier and quicker to implement in a multicentre clinical trial.

Chapter 3 summary

Chapter 3.3 described the patterns of cortical thinning in PNFA and SD – as hypothesized the cross-sectional results are broadly in keeping with previous studies using other techniques i.e. that the predominant areas of cell loss are in the anteroinferior temporal lobes in SD and the left inferior frontal lobe/insula in PNFA. The use of anomia as a measure of severity allowed investigation of the patterns of cell loss with increasing disease burden. Whilst this is not equivalent to a longitudinal study looking at changes with increasing disease duration, it is likely to provide broadly similar results. Longitudinal studies of PNFA and SD are lacking and both this part of Chapter 3.3 and also Chapter 3.4 provide more information about changes over time – in SD there is increasing spread of disease throughout the left hemisphere into more posterior temporal areas, as well as frontal and anterior cingulate lobes as well as spread into the right temporal lobe (which has, by the total millilitres lost a greater volume loss per year than the left temporal lobe). Although there is greater right temporal lobe involvement measures of hemisphere volume change show that there is in fact increasingly greater loss in the left hemisphere than the right hemisphere as a whole over time in SD. This is also the case for PNFA, which may have greatest atrophy in the inferior frontal lobe and insula but spreads throughout the left hemisphere to involve more of the frontal lobe as well as the temporal, particularly superior temporal lobe, and to a lesser extent anterior parietal lobe. Whilst whole brain measures are relatively simple and are currently used most commonly as secondary disease outcome measures in clinical trials of Alzheimer's disease, it may be that a region of interest may provide smaller sample sizes in the progressive language disorders but more work is necessary to look at faster, more automated measures.

4. Genetics and pathology of language impairment in FTLD

Although FTLD is commonly described in terms of its clinical syndrome i.e. behavioural variant frontotemporal dementia (bvFTD) and the language variants PNFA and SD, the underlying genetic and pathological basis of these disorders is heterogeneous without a clear one-to-one clinico-genetic or clinico-pathological correlation. It is often familial and there are five genes which are currently known to cause FTLD of which two are relatively common (microtubule-associated protein tau, *MAPT*, and progranulin, *GRN*) and three are rare causes (valosin-containing protein, *VCP*, chromatin modifying protein 2B, *CHMP2B*, and the gene encoding TDP-43 protein, *TARDP*) (Mackenzie et al, 2007; Benajiba et al, 2009). Pathologically, there are four main pathological subtypes characterized by which protein is found in cellular inclusions. Traditionally, FTLD pathology was split into those with tau-positive pathology, which includes corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and Pick's disease and those with tau-negative, ubiquitin-positive pathology, FTLD-U. However, more recently FTLD-U has been shown to consist mostly of patients with inclusions containing the protein TDP-43 (FTLD-TDP, which can be subtyped even further into types 1 to 4) with a minority of patients having inclusions containing the protein FUS (FTLD-FUS) and an even smaller number with a yet unknown disease-causing protein (called FTLD-UPS after the ubiquitin-proteosome system which is known to be involved albeit not the disease causing proteins) (Cairns et al, 2007; Mackenzie et al, 2009; Neumann et al, 2009). In terms of genetic-pathological correlations, MAPT mutations are associated with FTLD-tau whilst *GRN, VCP, TARDP* and *CHMP2B* mutations are associated with FTLD-U: *GRN*, *VCP* and *TARDP* mutations with FTLD-TDP and *CHMP2B* with FTLD-UPS.

After a review of previous studies (4.1), this chapter will initially look at the heritability of the different FTLD clinical syndromes (and in particular the language subtypes) and the extent to which the currently known mutations account for that heritability (4.2). The two common genetic mutations (*GRN* and *MAPT*) are then compared in terms of neuropsychological and particularly imaging features (4.3). In the last chapter (4.4) the clinico-pathological correlation of language impairment in FTLD is examined.

The specific hypotheses of Chapter 4 are:

1. There will be variable heritability of the different clinical subtypes of FTLD and the language subtypes will be less familial than the behavioural variant of frontotemporal dementia.
2. The different progressive aphasias will be associated with differing genetic and pathological causes.
3. On a nonfluent aphasia versus semantic dementia dichotomy there will not be a one-to-one clinico-pathological correlation.
4. Different genetic and pathological forms of FTLD will have differing patterns of atrophy and differing associations with particular clinical syndromes.

4.1 Overview of previous genetics and pathology studies

A number of studies have shown that FTLD is commonly familial (Stevens et al, 1998; Chow et al, 1999; Bird et al, 2003) with mutations in a number of different genes known to be causative of FTLD. Mutations were first discovered in the *MAPT* gene in 1998 (Hutton et al, 1998; Poorkaj et al, 1998; Spillantini et al, 1998) with mutations in *VCP* (Watts et al, 2004) and then *CHMP2B* (Skibinski et al, 2005) discovered in the mid 2000s. Mutations in these latter two genes are only rare causes of FTLD and it was not until 2006 that a more common genetic cause was found following discovery that mutations in the *GRN* gene on chromosome 17 caused FTLD, finally explaining the conundrum of genetic linkage of families with FTLD-U to a region including *MAPT* (Baker et al, 2006; Cruts et al, 2006). Although mutations in *MAPT* and *GRN* are the most common of the FTLD disease-causing genes there is variability in the prevalence geographically across different reported series: *MAPT* mutation frequency varies between 3 and 14% (Houlden et al, 1999; Rosso et al, 2003; Stanford et al, 2004; Signorini et al, 2004) and *GRN* mutation frequency varies between 1 and 16% in different series (Cruts et al, 2006; Gass et al, 2006; Le Ber et al, 2007; Pickering-Brown et al, 2008; Borroni et al, 2008b; Benussi et al, 2009) with some series reporting vastly different frequencies within the same country e.g. two studies of FTLD cohorts in Italy found frequencies of 1.6% and 15.2% (Borroni et al, 2008b; Benussi et al, 2009). Recent series have directly compared the frequency of *MAPT* and *GRN* mutations in FTLD populations (Cruts et al, 2006; Gass et al, 2006; Le Ber et al, 2007; Pickering-Brown et al, 2008: Table 4.1.1): some countries have families with a founder effect causing higher *GRN* mutation prevalence than *MAPT* e.g. in Belgium (Cruts et al, 2006). In the UK, the 10+16 *MAPT* mutation is common with a known founder effect (Pickering-Brown et al, 2004) which is likely to account for the higher frequency of *MAPT* mutations in some series (Pickering-Brown et al, 2008).

Table 4.1.1

Previously reported series comparing frequencies of *MAPT* and *GRN* mutations in an FTLD spectrum population

Series	Geographical area	Number in series	% MAPT mutations	% GRN mutations
Cruts et al, 2006	Belgium	103	1.9	10.7
Gass et al, 2006	USA	167	4.4	4.8
Le Ber et al, 2007	France	210	2.9	4.8
Pickering-Brown et al, 2008	UK	223	7.6	5.8

Age at onset appears to be variable in both *GRN* and *MAPT* mutations: for *GRN* the youngest patient thus far reported had an age of onset of disease of 35 (Leverenz et al, 2007) with the oldest case being 83 years old at onset (Gass et al, 2006) with wide variability even within the same family. Some studies of *GRN* mutations have shown evidence of non-penetrance which may be age-related (Gass et al, 2006). *MAPT* mutations appear to be fully penetrant with an age at onset between 30 and 70 (van Swieten et al, 2007).

While the clinical spectrum of both *MAPT* and *GRN* mutations is heterogeneous, certain features occur more frequently in association with a particular molecular substrate. Patients with *MAPT* mutations commonly present with bvFTD which may be accompanied by a corticobasal syndrome (CBS) or more rarely a progressive supranuclear palsy (PSP) syndrome (van Swieten et al, 2007). Cognitively, executive dysfunction is widely recognized but patients commonly develop semantic impairment later in the disease (Pickering-Brown et al, 2008) as well as prominent episodic memory difficulties (van Swieten et al, 2007). Patients with *GRN* mutations also present most commonly with bvFTD and there may be an associated CBS (van Swieten et al, 2008). However, unlike *MAPT* mutations patients in this group frequently present with one of the language variants of FTLD (van Swieten et al, 2008; Pickering-Brown et al, 2008).

Clinico-pathological correlation in FTLD is similarly not one-to-one although there are a number of emerging patterns from more recent studies. The behavioural variant of FTLD appears to be associated with each of the different pathological subtypes with none being over-represented. The language variants SD and PNFA however do appear to show some clearer associations with particular pathologies. SD seems to be most commonly caused by FTLD-TDP (with the original studies showing association with FTLD-U and more recent studies showing that this is the FTLD-TDP subtype: Rossor et al, 2000; Davies et al, 2005; Knibb et al, 2006; Snowden et al, 2007a; Pereira et al, 2009) although cases of FTLD-tau Pick's disease and Alzheimer's pathology have been more rarely reported. PNFA can be caused by both FTLD-tau and FTLD-TDP pathologies, although patients with a prominent motor speech impairment are associated particularly with the FTLD-tau pathologies, corticobasal degeneration, progressive supranuclear palsy and Pick's disease (Josephs et al, 2006) rather than FTLD-TDP. However, a single case of progressive motor speech impairment and Alzheimer pathology is also reported (Gerstner et al, 2007).

4.2 The genetics and heritability of FTLD

The initial study in this Chapter set out to look at the heritability of FTLD in each of the different clinical syndromes and to investigate to what extent the known genes account for this heritability, and which clinical syndromes they are associated with.

METHODS

Sample collection

Blood was collected for DNA extraction with written consent from patients attending the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London and also from patients involved in studies of FTLD at the Dementia Research Centre, Institute of Neurology, Queen Square, London. Prior to the onset of this study a cohort of 100 DNA samples were available for study and a further 125 samples were collected during the period of this study i.e. in total 225 samples of patients who had a diagnosis within the FTLD spectrum (the canonical clinical syndromes of bvFTD, PNFA and SD as well as FTD-MND, CBS and PSP) according to consensus criteria (Neary et al, 1998; Boeve et al, 2003b; Litvan et al, 1996).

Analysis of family history

A measure of family history was devised by adapting a score used in Goldman et al, 2005 where 1 is an autosomal dominant family history of FTLD, MND, CBS or PSP, defined as the presence of at least three affected people in two generations with one person being a first-degree relative of the other two, 2 is familial aggregation of three of more family members with dementia but not meeting criteria for 1, 3 is one other affected family member with dementia and 4 is no or unknown family history. This was modified by changing a score of 3 into two separate scores: 3 only if there was a history of young-onset dementia within the family i.e. less than 65, and 3.5 if onset was above 65 All patients were given a "modified Goldman score" between 1 and 4 based on this scale. All patients had had a structured clinical interview which had included a detailed family tree. This had been discussed with the patient and family members (a minimum of one other person). The data for this study were ascertained from a

review of all of the clinical notes: data were available on 222 of the cases with only 3 patients scoring 4 because of an unknown family history (2 with bvFTD and 1 with FTD-MND).

Genetic analysis

All 225 patients were screened for mutations in *MAPT* and *GRN* detecting 39 pathogenic mutations. Of the remaining 186 mutation negative patients, sequencing was obtained for *VCP* exons 3, 5, 6 and 10 in 160 patients, *TARDBP* exons 4 and 6 in 179 patients, and *CHMP2B* in 92 patients. Exon 15 of the FUS gene was also sequenced in 183 patients, mutations in which have been previously shown to be causative of motor neurone disease, although currently no mutations have been found in FTLD (Vance et al, 2009; Kwiatkowski et al, 2009).

RESULTS

Demographic and family history data (Table 4.2.1)

Almost half of the 225 patients had bvFTD as their initial clinical syndrome (44.4%) with the next most common disorders being PNFA (20%) and SD (16.0%). Smaller numbers had CBS or a CBS/PNFA overlap syndrome, PSP or FTD-MND. Average age of onset for the different groups was between 54.8 years (bvFTD) and 61.6 years (PNFA) with a total mean of 57.3 years. In total 58.2% of the patients were male with more male patients in each of the groups apart from the CBS and CBS/PNFA overlap groups. 10.2% of patients had an autosomal dominant inheritance (as defined by a modified Goldman score of 1) but the heritability of FTLD was substantially higher (41.8%) when a family history was defined by a modified Goldman score of 1, 2, 3 or 3.5). The bvFTD group had the largest proportion of cases with a family history (58.0% with modified Goldman score 1 to 3.5 and an average modified Goldman score of 2.9) and the least familial of the disorders were FTD-MND (10.0%, 3.8) and SD (22.2%, 3.8) (Table 4.2.1).

Table 4.2.1

Demographic and family history data for the cohort of 225 FTLD patients (n = number of cases, AAO = age at onset of symptoms)

Initial clinical syndrome	n	% of total cases	Average AAO	%male	Modified Goldman score (% of cases)					% of cases with score 1-3.5	Average score
					1	2	3	3.5	4		
SD	36	16.0	57.9	52.8	0.0	5.6	5.6	11.1	77.8	22.2	3.8
PNFA	45	20.0	61.6	62.2	2.2	1.1	0.0	13.3	73.3	26.7	3.6
PNFA/CBS	8	3.6	61.3	12.5	12.5	0.0	12.5	12.5	62.5	37.5	3.4
bvFTD	100	44.4	54.8	64.0	20.0	17.0	11.0	10.0	42.0	58.0	2.9
FTD-MND	10	4.4	56.7	70.0	0.0	10.0	0.0	0.0	90.0	10.0	3.8
CBS	17	7.6	57.6	41.2	5.9	11.8	17.6	17.6	47.1	52.9	3.3
PSP	9	4.0	58.9	55.6	0.0	33.3	0.0	0.0	66.7	33.3	3.3
Total	**225**		**57.3**	**58.2**	**10.2**	**13.3**	**7.6**	**10.7**	**58.2**	**41.8**	**3.5**

Genetic analysis

Mutations were found in the *MAPT* and *GRN* genes but no mutations were found in the *CHMP2B, VCP*, *TARDBP* or *FUS* genes. In total 20 patients (8.9%) had mutations in *MAPT* (15 probands) and 19 patients (8.4%) had mutations in *GRN* (13 probands). Of the *MAPT* mutations, thirteen (from eight families) had an intronic 10+16 mutation of which seven families had previously been described (Janssen et al, 2002). The other previously described mutations were an intronic 10+19 mutation as well as deltaK280, L284R, N296N (Spillantini et al, 2000), S320F and G389R mutations. A novel MAPT variant was also found, N286N, a synonymous change similar to the N296N which is thought to be pathogenic via its effect on the splicing of exon 10. Most patients presented with bvFTD (although many developed semantic impairment as the disease progressed) apart from the N296N (CBS) and the L284R (PSP) mutations. The *GRN* mutations were ten C31fs mutations (from four families) and two

Q130fs mutations (from two families). Other mutations were S203fs, E498fs, Q300X, L469F, A199V mutations as well as 1048_1049insG and R493X mutations. Patients were diagnosed with bvFTD (C31fs, Q130fs, Q300X), PNFA (C31fs, L469F, R493X, S203fs) or CBS (1048_1049insG, A199V, C31fs, E498fs) with two patients having a PNFA/CBS overlap (C31fs, E498fs).

Of the 186 patients without a known mutation the number of cases with a family history were re-examined and in particular it was looked at whether any of the "familial" cases had post-mortem confirmation of FTLD pathology (Table 4.2.2). The majority of these cases (125) had a modified Goldman score of 4 but four cases with an autosomal dominant family history (modified Goldman score of 1) were still without a known mutation (all with bvFTD) and in total 61 cases with a modified Goldman score of 1,2,3, or 3.5 were not known to have a mutation. These included a small number of cases with either PNFA or SD (with 2 in each group having a modified Goldman score of 2). Those cases with a score of 1, 2 or 3 (38 in total) were looked at in particular as a score of 3.5 may well represent another family member with old-age onset dementia and therefore less likely to be a true familial history of FTLD. Of these 38 cases seven had pathological confirmation of disease (6 bvFTD and 1 FTD-MND). All of these cases had tau-negative FTLD pathology: 1 case with bvFTD was known to have ubiquitin-positive, TDP-43 negative, FUS-negative pathology (FTLD-UPS) without intranuclear inclusions similar to the pathology found in the Danish family with a mutation in *CHMP2B* (but in this case without a *CHMP2B* mutation) but the other six all had FTLD-TDP (i.e. TDP-43 pathology) with all having type 3 pathology according to consensus criteria (Cairns et al, 2007).

Table 4.2.2

Number of cases without mutations stratified according to their family history.

	Modified Goldman score (n cases)					TOTAL (n)
	1	**2**	**3**	**3.5**	**4**	
SD	0	2	2	4	27	35
PNFA	0	2	0	6	31	39
PNFA/CBS	0	0	0	1	5	6
bvFTD	4	15	7	9	39	74
FTD-MND	0	1	0	0	9	10
CBS	0	1	2	3	8	14
PSP	0	2	0	0	6	8
Total	**4**	**23**	**11**	**23**	**125**	**186**

DISCUSSION

The results of this study confirm previous findings that FTLD is a highly heritable degenerative disorder. However, heritability varies between the different clinical syndromes with SD having a much lower percentage of cases with a family history compared with bvFTD. A previous study suggested that FTD-MND was the most heritable of the FTLD syndromes (Goldman et al, 2005) but in this series it was the least heritable, albeit with low numbers in this cohort. Inconsistent results with other series may reflect ethnogeographic clustering of particular causal mutations. Numbers were also low in the PSP group limiting the ability to interpret these data.

Mutations in *MAPT* and *GRN* are relatively common and have a similar prevalence in our series. The 10+16 *MAPT* mutation founder effect in the UK accounts for a relatively higher proportion of *MAPT* mutations compared to other reported series outside of the UK (Table 4.1.1) but genetic studies seem to show that patients in this series with the *GRN* C31fs mutation are part of the same family, which is likely to at least partly account for the similar prevalence of *GRN* and *MAPT* mutations in this series.

No mutations were found in *VCP, CHMP2B* or *TARDP* consistent with previous series suggesting that these are rare causes of FTLD. It remains possible that causal mutations in these genes are present in unscreened exons of these 3 genes, although the sequencing strategy covered all known mutations to date. No mutations were also found in *FUS* suggesting that mutations in this gene are either not causative or are a very rare cause of FTLD.

Taking into account the known mutations many patients were still found to have a strong family history suggesting that there are still unknown genes that cause FTLD (Seelaar et al, 2008). One locus (on chromosome 9) is known for patients with a clinical phenotype of FTD-MND (Le Ber et al, 2009), however this is associated with type 2 FTLD-TDP. Analysis of the pathological cases within this subgroup suggests that there are at least two other groups of patients with a family history without a known mutation: those with FTLD-UPS and those with type 3 FTLD-TDP without a *GRN* mutation (some of whom have a clinical phenotype of FTD-MND). Although similar pathologically to cases with *CHMP2B* mutations, the single case in our series was negative for mutations in this gene. Studies of type 3 FTLD-TDP suggest that between 30 and 60% of such patients have *GRN* mutations but some patients negative for *GRN* mutations still have a family history (Josephs et al, 2007; Geser et al, 2009; Josephs et al, 2009). There are no known loci associated with such patients suggesting further work needs to be done to clarify the genetic cause in this group as well as patients with familial FTLD-UPS.

From the point of view of the language variants, whilst some cases of PNFA are associated with *GRN* mutations, there are still a small number of language cases (both PNFA and SD) with a strong family history and without mutations in the known disease-causing genes. Therefore it is likely that certain critical genetic determinants of language breakdown are yet to be discovered. However, taking these results together as a whole, it is clear that a simple genetic (Mendelian) contribution to the development of language syndromes is relatively small. It is therefore likely that there are multiple genetic and epigenetic factors that operate in the eventual development of a progressive aphasia in a single individual.

4.3 A comparison of the neuropsychological and imaging features of progranulin and tau mutations

There are few studies looking at the neuropsychological and/or imaging features of both *GRN* and *MAPT* mutations (Whitwell et al, 2007a; Ghetti et al, 2008; Pickering-Brown et al, 2008; Whitwell et al, 2009) although initial reports suggest that *GRN* mutations are associated with a clinical syndrome of bvFTD, PNFA or CBS whilst *MAPT* mutations are associated with bvFTD and later semantic impairment. This study investigated the demographic, neuropsychological and imaging features of *GRN*-associated FTLD in comparison to *MAPT*-associated FTLD.

METHODS

Subjects

In Chapter 4.2 from the total cohort of 225 DNA samples, 20 patients (from 15 families) were found to have *MAPT* mutations and 19 patients (from 13 families) had *GRN* mutations. Age at onset and disease duration data were available from these patients and also six further members of *MAPT* mutation families and six further members of *GRN* mutation families. A retrospective review of the Specialist Cognitive Disorders Clinic database was undertaken to assess how many of these patients had cross-sectional neuropsychology and imaging data and therefore would be included in the main part of the study. Eleven patients with a *MAPT* mutation (mean (standard deviation) age at baseline scan 53.5 (5.2)) and nine patients with a *GRN* mutation (mean (standard deviation) age at baseline scan 62.9 (6.1)) were included in the study: the *MAPT* mutation group comprised 8 patients with a 10+16 mutation and single patients with 10+14, S320F and G389R mutations; the *GRN* mutation group comprised four patients with a C31fs mutation, two patients with a Q130fs mutation and single patients with A199V, S203fs and E498fs mutations.

Demographic data for these patients are shown in Table 4.3.1. All patients with *MAPT* mutations presented initially with a bvFTD syndrome whilst patients with *GRN* mutations presented with bvFTD, PNFA or CBS. A control group of fifteen cognitively-normal controls (10 males, 5 females) were used for comparison in the imaging study (mean (standard deviation)

age at baseline scan 57.5 (5.3)). All patients included in the study had at least one volumetric brain MRI scan; six patients with a *MAPT* mutation and four patients with a *GRN* mutation had two scans.

Neuropsychology testing

Neuropsychological assessment consisted of a battery of cognitive tests. Verbal and visual episodic memory had been tested using the Recognition Memory Tests for Words and Faces respectively (Warrington, 1984; Warrington, 1996) whilst naming had been assessed with the Graded Naming Test (McKenna et al, 1980). Other cognitive domains that had been assessed were spelling (Graded Difficulty Spelling Test, Baxter et al, 1994), calculation (WAIS-R Arithmetic, Wechsler, 1981) and visuospatial and visuoperceptual skills (subtests of the Visual Object and Spatial Perception (VOSP) battery: Warrington et al, 1991). Executive function was assessed using a Modified Card Sorting test or the Weigl test (Nelson, 1976; Weigl, 1948). The presence or absence of limb apraxia was also noted. Patients were said to have a deficit in a particular cognitive domain if they scored below the 5th percentile on the test and their score was thought to represent a true deficit in that domain rather than being secondary to other factors such as concentration or attention.

Imaging analysis

Brain image acquisition as well as volumetric whole brain and hemisphere imaging methods and voxel-based morphometry methods are as described in Chapter 2. For VBM, linear regression models were used to examine differences in GM and WM volume between the groups. Voxel intensity, V, was modelled as a function of group, and subject age gender and total intracranial volume were included as nuisance covariates. $V=\beta_1$ *MAPT* carriers + β_2 *GRN* carriers + β_3 controls + β_4 age + β_5 gender + β_6 TIV + μ + ε (where μ is a constant, and ε is error). Separate analyses were performed on the grey and white matter segments. Maps showing statistically significant differences between the groups were generated, correcting for multiple comparisons in the disease group-control comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.001 significance level. For disease group comparisons no differences were seen at such a strict correction and maps were

generated uncorrected at a 0.001 significance level. Statistical parametric maps were displayed as overlays on a study-specific template, created by warping all native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

In order to visualise hemispheric asymmetries, two VBM analyses were performed: firstly with all images in their native space; and secondly, with native images flipped in the midsagittal plane within SPM5, such that the most severely affected cerebral hemisphere was on the same side in each patient. An image was selected for flipping if it had an hemispheric asymmetry index outside the control range and more severe right hemisphere atrophy (i.e. images were flipped such that any asymmetric atrophy was displayed on the left): four images from the GRN group and three from the MAPT group met criteria for flipping

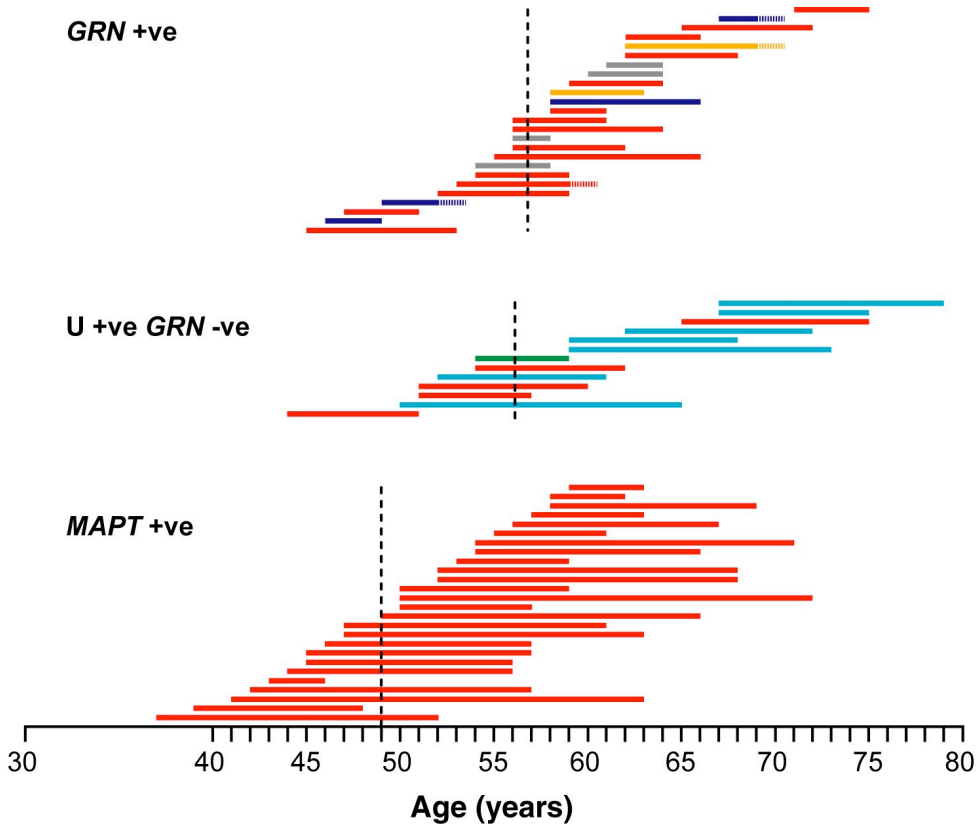
RESULTS

Age at onset and disease duration

Age at onset or death were available for 25 *GRN* mutation carriers and were compared with 26 *MAPT* mutation carriers as well as 15 cases with FTLD-U pathology at autopsy (4 familial and 11 sporadic) but no *GRN* mutation (Figure 4.3.1). Mean (standard deviation) age at onset for *GRN* was 57 (3) years, eight years later than for *MAPT* at 49 (2) years (t-test, two-tailed, $p = 8.3 \times 10^{-5}$). However, age at onset was similar between *GRN* and FTLD-U with no *GRN* mutation (*GRN* –ve age at onset 56 (3) years, t-test, two-tailed, p = 0.73). *GRN* carriers had a much shorter clinical duration than other subtypes of FTLD. Mean clinical duration for *GRN* was 5 (1) years compared with *MAPT* 12 (2) years (t-test, two-tailed, $p = 7.8 \times 10^{-6}$) and FTLD-U with no *GRN* mutation 9 (2) years (t-test, two-tailed, p = 0.002). Across these three aetiological subgroups, a later age at onset was associated with a shorter clinical duration (p = 0.006). A linear regression model was fitted to question the proportion of the variation in clinical duration accounted for by aetiological subgroup and/or age at onset. The model with minimal residual that best accounted for clinical duration incorporated aetiological subgroup and age at onset ($p = 6.5 \times 10^{-6}$), this model accounted for 34% of the variance of clinical duration.

Figure 4.3.1

Age at onset, age at death and duration of disease are shown in the *GRN* mutation carriers (*GRN* +ve), *MAPT* mutation carriers (*MAPT* +ve) and *GRN-negative* FTLD-U (U+ GRN-ve). The dotted vertical line indicates the mean age at clinical onset for each group. Red lines = bvFTD, dark blue lines = PNFA, light blue lines = SD, yellow lines = CBS, grey = 'dementia' unspecified.



Clinical features

In the *GRN* cohort, the main clinical diagnoses were bvFTD, PNFA and CBS with one patient having a PNFA/CBS overlap. Amongst those presenting with behavioural symptoms, the most common initial feature was apathy. Other common behavioural features included abnormal eating behaviour (generally a sweet tooth) and inappropriate social behaviour with lack of insight. Some patients developed disinhibition later in the illness but this was rarely a presenting feature. Less common symptoms included loss of empathy, aggression, obsessive behaviour (including hoarding), impulsivity and hypersomnolence. One patient had tactile hallucinations of insects crawling over his skin with delusions that there were animals present in his bed to the extent that he refused to sleep in his bedroom. Many of the patients with

bvFTD had decreased quantity of speech without evidence of speech errors, agrammatism or articulatory impairment. Six of these patients had become mute when last seen. This language impairment would be consistent with dynamic aphasia rather than either the progressive non-fluent aphasia or semantic dementia subtype of FTLD. None of the patients had evidence of motor neuron disease whilst 5 of the patients had features of parkinsonism (56%).

In the *MAPT* cohort all of the patients had an initial diagnosis of bvFTD with the most common initial feature being disinhibition although the other common behavioural features of bvFTD were seen as the disease progressed similar to *GRN* mutations. Delusions and hallucinations were not seen in this group and neither was a primary language impairment. However, 6 of the patients developed features of parkinsonism (55%) similar in frequency to the *GRN* cohort.

Neuropsychological features (Table 4.3.1)

Many patients in both the *GRN* and *MAPT* groups performed poorly on tests of episodic memory and although failure on these tests could in principle be due to a number of factors most of these patients also complained of amnestic symptoms. Executive function was variably affected in both groups but naming was more commonly affected in the *MAPT* mutations group with errors being noted to be mainly semantic errors. Data that were available on this group of patients suggested that as well as the anomia patients also developed impairment of single word comprehension, which together suggest the development of semantic impairment. Impaired calculation, limb praxis, spelling, visuospatial or visuoperceptual skills were seen in the *GRN* patients. These features are generally considered markers of parietal lobe dysfunction and all *GRN* cases had at least one such deficit, compared with the *MAPT* group where only one patient had a parietal lobe deficit. To investigate this further the presence of parietal lobe deficits in this group were compared with the rest of the DNA sample cohort decribed in Chapter 4.2. Neuropsychological data were available for 121 *GRN*-negative patients from this cohort: the presence of dyscalculia, limb apraxia, spelling problems and visuospatial or visuoperceptual impairments was specifically assessed. Whilst in the *GRN* group 100% of the patients with definite mutations had at least one deficit attributable to parietal lobe dysfunction, in the *GRN*-ve FTLD-U group there were 25% (4/16) (chi-squared test *GRN* vs *MAPT*, 1 d.f., p

= 6.8 x 10^{-6}; *GRN* vs. FTLD-U, 1 d.f., p = 7.0 x 10^{-6}). Looking at the 121 *GRN* -ve patients by clinical diagnosis the percentage of cases with parietal lobe deficits was 100% in CBS (15/15) with all having limb apraxia, 32% in the bvFTD group (18/56), 36% in SD (8/22) and 43% in PNFA (12/28). This emphasizes that there is greater parietal lobe involvement in *GRN*-associated FTLD than in other FTLD groups with the exception of CBS, a disorder known to involve frontal and parietal lobes (and clinically, generally defined by the presence of a parietal deficit, namely apraxia).

Table 4.3.1 Neuropsychological features of *MAPT* and *GRN* mutation carriers. Verbal IQ (VIQ) and Performance (PIQ) scores are taken from the WAIS-R. Recognition Memory Test (RMT) for Words and Faces, Graded Naming Test (GNT), Graded Difficulty Spelling Test (GDST), WAIS-R arithmetic and Visual Object and Space Perception (VOSP) battery results are quoted in percentile scores where a score below the 5th percentile is considered impaired. Of note, the VOSP scores are heterogeneous as different subtests of the battery were used in different patients. Executive function tasks are the Weigl or Wisconsin Modified Card Sorting Tasks or the Stroop task and are quoted as pass or fail. Limb apraxia is quoted as present or absent.

Patient	Presenting syndrome	Mutation	Gender	Age at scan	Duration at scan	VIQ	PIQ	RMT WORDS	RMT FACES	GNT	GDST	WAIS-R arithmetic	Limb apraxia	VOSP	Executive function
MAPT1	bvFTD	10+16	M	54.5	7.5	91	96	<5th	<5th	<5th	10-25th	50-75th	-	<5th	Fail
MAPT2	bvFTD	10+16	M	58.0	8.0	97	107	<5th	<5th	<5th	50-75th	50-75th	-	>50th	Pass
MAPT3	bvFTD	S320F	M	58.7	7.7	107	128	>75th	5-10th	<5th	NT	>75th	-	25-50th	Pass
MAPT4	bvFTD	G389R	M	46.1	3.1	77	70	<5th	<5th	<5th	25-50th	25-50th	-	>10th	Fail
MAPT5	bvFTD	10+16	F	48.8	6.8	83	81	10-25th	<5th	<5th	NT	10-25th	-	50-75th	Fail
MAPT6	bvFTD	10+16	F	53.2	3.2	90	84	10-25th	<5th	<5th	10-25th	25-50th	-	25-50th	Fail
MAPT7	bvFTD	10+14	M	50.1	9.1	100	96	<5th	<5th	<5th	NT	>75th	-	NT	NT
MAPT8	bvFTD	10+16	M	52.5	5.5	104	121	5-10th	5-10th	<5th	NT	>75th	-	>75th	Pass
MAPT9	bvFTD	10+16	M	45.9	8.9	99	93	<5th	<5th	5-10th	NT	>75th	-	>5th	Pass
MAPT10	bvFTD	10+16	M	60.7	2.7	99	105	<5th	<5th	<5th	NT	50-75th	-	>10th	Fail
MAPT11	bvFTD	10+16	F	56.8	1.8	85	97	<5th	25-50th	50-75th	NT	5-10th	-	>5th	Pass
GRN1	bvFTD	C31fs	M	67.4	1.4	84	72	<5th	<5th	10-25th	10-25th	10-25th	+	<5th	Fail
GRN2	bvFTD	Q130fs	F	65.5	3.5	59	74	<5th	<5th	<5th	10-25th	<5th	-	<5th	Fail
GRN3	PNFA	C31fs	F	68.3	2.3	85	108	50-75th	10-25th	<5th	NT	NT	+	25-50th	Pass
GRN4	bvFTD	Q130fs	M	65.9	3.9	107	95	25th	10-25th	>75th	NT	>75th	+	>5th	Fail
GRN5	PNFA	C31fs	F	63.0	5.0	84	86	10-25th	<5th	25-50th	10-25th	<5th	+	25-50th	Fail
GRN6	PNFA	S203fs	M	50.6	2.6	66	98	25-50th	>75th	<5th	<5th	<5th	-	>50th	Pass
GRN7	bvFTD	C31fs	M	56.4	3.4	88	80	25-50th	25-50th	50-75th	NT	10-25th	+	>50th	Fail
GRN8	PNFA/CBS	E498fs	F	68.4	6.4	Unable	69	5-10th	<5th	<5th	NT	5-10th	+	<5th	NT
GRN9	CBS	A199V	M	60.7	5.7	61	Unable	Unable	Unable	<5th	NT	<5th	+	<5th	Fail

Volumetric imaging data

Whole brain volumes and rate of atrophy

Baseline brain volumes were smaller in both disease groups compared with healthy controls and mean brain volume was significantly smaller in the *GRN* group compared with the *MAPT* group (Table 4.3.2). Rates of whole brain atrophy were significantly greater in the *GRN* group with no overlap with the *MAPT* group (Table 4.3.2, Figure 4.3.2).

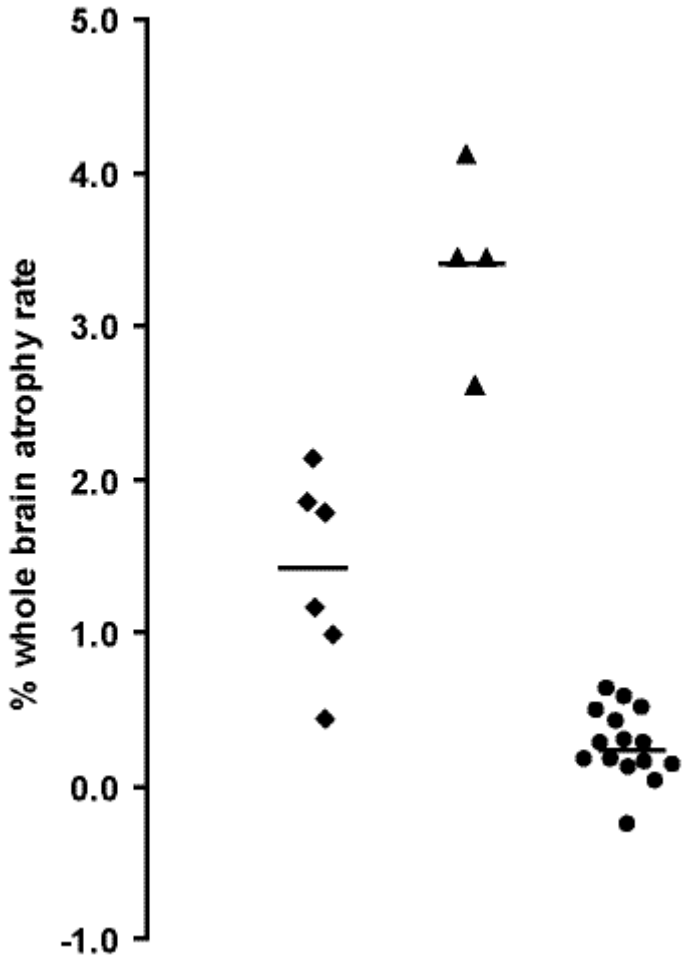
Table 4.3.2

Volumetric cross-sectional and longitudinal data for whole brain and hemisphere volumes ([a]p<0.05 disease group significantly worse than. controls, [b]p<0.05 *GRN* mutation group significantly worse than *MAPT* mutation group)

Mean (95% confidence intervals)	***MAPT* mutations**	***GRN* mutations**	**Controls**
Whole brain volume (ml)	1117.3 (1079.6, 1162.5)[a]	996.8 (914.0, 1099.2)[a, b]	1230.5 (1180.2, 1272.6)
Whole brain BSI atrophy rate (%/yr)	1.4 (0.9, 1.9)[a]	3.4 (2.8, 4.0)[a, b]	0.3 (0.1, 0.4)
Left hemisphere volume (ml)	553.5 (536.4, 573.4)[a]	496.4 (460.8, 545.4)[a, b]	605.2 (581.3, 626.3)
Right hemisphere volume (ml)	552.0 (531.8, 574.9)[a]	489.8 (437.0, 562.1)[a]	605.9 (581.6, 625.3)
Left/right hemisphere ratio	1.00 (0.99, 1.02)	1.03 (0.93, 1.15)	1.00 (0.99, 1.01)

Figure 4.3.2

Annualized rates of whole brain atrophy (as measured using the boundary shift integral) in the MAPT mutation (diamonds) and GRN mutation (triangles) groups as well as the controls (circles).



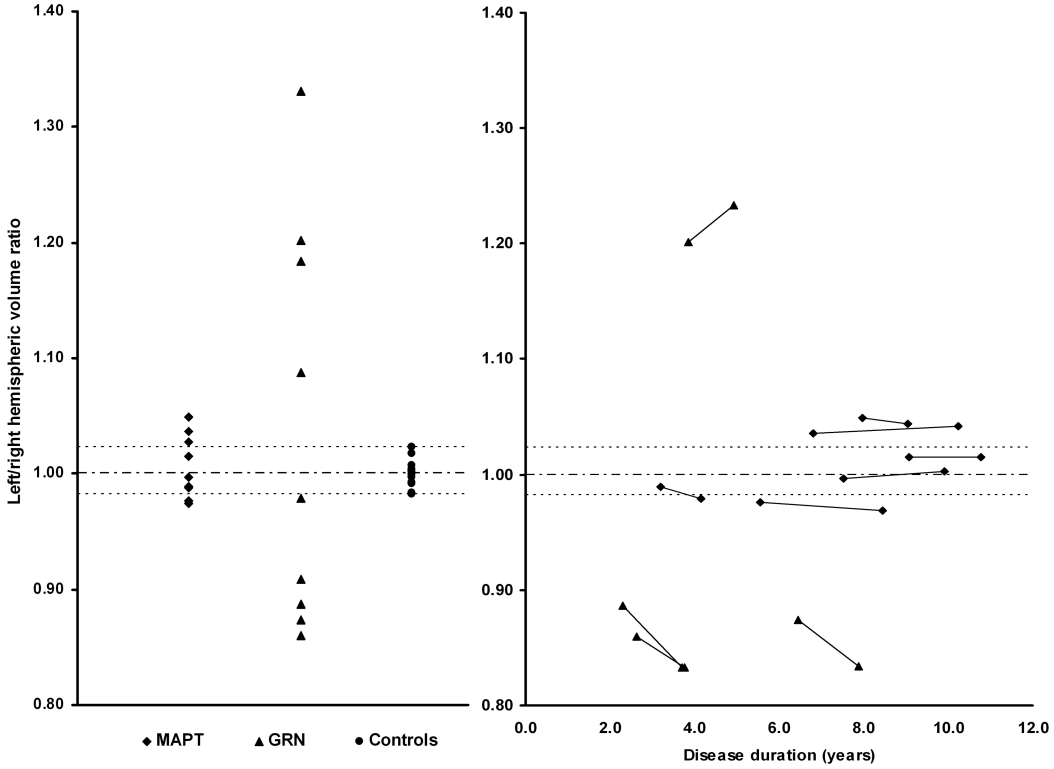
Hemisphere volumes

Baseline mean left and right hemisphere volumes were smaller in the disease groups than the controls and mean left hemisphere volume was significantly smaller in the *GRN* group compared with the *MAPT* group, with a trend to smaller mean right hemisphere volume in the *GRN* group (p=0.07) (Table 4.3.2, Figure 4.3.3A). The overall mean left/right asymmetry ratio was similar in all three groups, however individual cases in the *GRN* group were highly asymmetrical with all cases falling outside of the control range (Figure 4.3.3A), whereas the *MAPT* group were most often symmetrical with a few cases just falling outside the control range. Only a single *GRN* patient (GRN5) fell within the range of values of the *MAPT* group.

Furthermore, in the patients with longitudinal imaging, *GRN* cases became more asymmetric as the disease progressed whilst *MAPT* patients remained similarly symmetrical (Figure 4.3.3B).

Figure 4.3.3

Left/right hemisphere volume ratio in the three groups (A) and in patients with longitudinal imaging as a function of disease duration (B)



VBM data

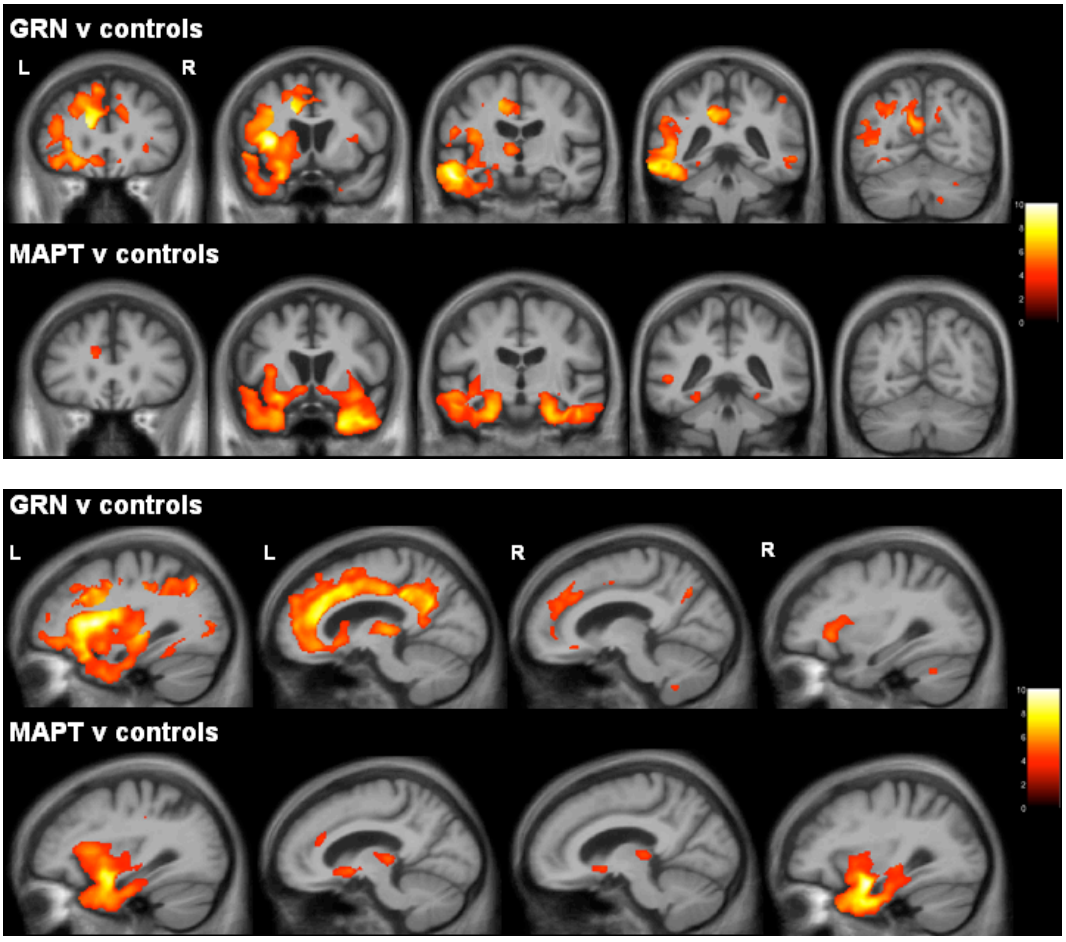
Grey matter atrophy in disease groups versus controls

Patterns of grey matter atrophy differed in the *MAPT* and *GRN* groups compared with healthy controls (Figure 4.3.4). The *GRN* group analysis on unflipped images showed an overall pattern of symmetrical atrophy in a brain network including frontal, temporal and parietal lobes, cingulate cortex and thalamus. However, this result obscures any asymmetries in favour of left or right hemisphere at individual subject level: after flipping of images so that all patients had the most affected hemisphere in the same orientation the true asymmetry of *GRN* disease was apparent (Figure 4.3.4). The most significant areas of grey matter atrophy were in the inferior frontal lobe [-40, 21, 4], dorsal insula [-32, 11, 7], superior temporal gyri [-47, 3, -9], middle

temporal gyri [-57, -23, -12], dorsal anterior cingulate cortex [-10, 32, 18], precuneus [-11, -54, 25] and inferior parietal lobe [-47, -54, 22]. In contrast, the MAPT group analysis on flipped images revealed symmetrical involvement of a distinct and more ventral network including anterior temporal [-36, 10, -25; 36, 10, -26] and medial temporal lobes [-20, -8, -16; 24, -8, -19], orbitofrontal cortex [-20, 8, -14; 31, 8, -11] and ventral insula [-34, -1, -2; 34, 0, -1] with less involvement of the anterior cingulate [-11, 29, 19] (Figure 4.3.4).

Figure 4.3.4

VBM analysis on grey matter (GM) regions in *GRN*- and *MAPT*-associated FTLD relative to healthy controls. The colour bar (lower right) indicates the t score. Left (L) and right (R) markers are shown for ease of reference however this analysis was performed on flipped images (see above).



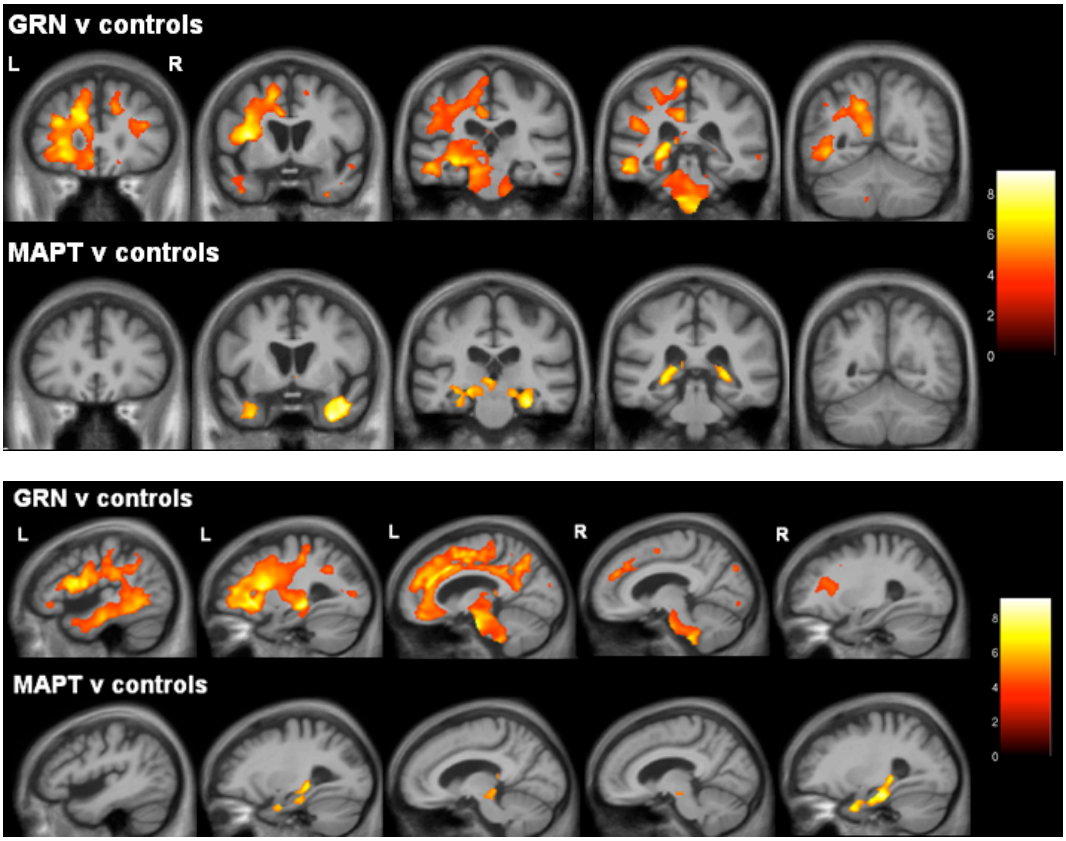
White matter atrophy in disease groups versus controls

In the *GRN* group compared with controls, the white matter VBM analysis showed most significant involvement of areas likely to be within intrahemispheric long association tracts

including inferior longitudinal fasciculus [-46, -37, -11], superior longitudinal fasciculus [-30, 9, 12], inferior fronto-occipital fasciculus [-25, 21, -9] and cingulum [-19, 21, 27]. There was additional involvement of the corpus callosum and brainstem tracts, particularly in the pons (Figure 4.3.5). In the *MAPT* group compared with controls, the most significant areas of white matter loss lay in the fornices bilaterally [-21, -18, -12; -20, -34, 3] with less marked involvement of the uncinate fasciculus [30, 3, -33; -32, -1, -30] (Figure 4.3.5).

Figure 4.3.5

VBM analysis on white matter (WM) regions in *GRN*- and *MAPT* associated FTLD relative to healthy controls. The colour bar (lower right) indicates the t score. Left (L) and right (R) markers are shown for ease of reference however this analysis was performed on flipped images (see above).



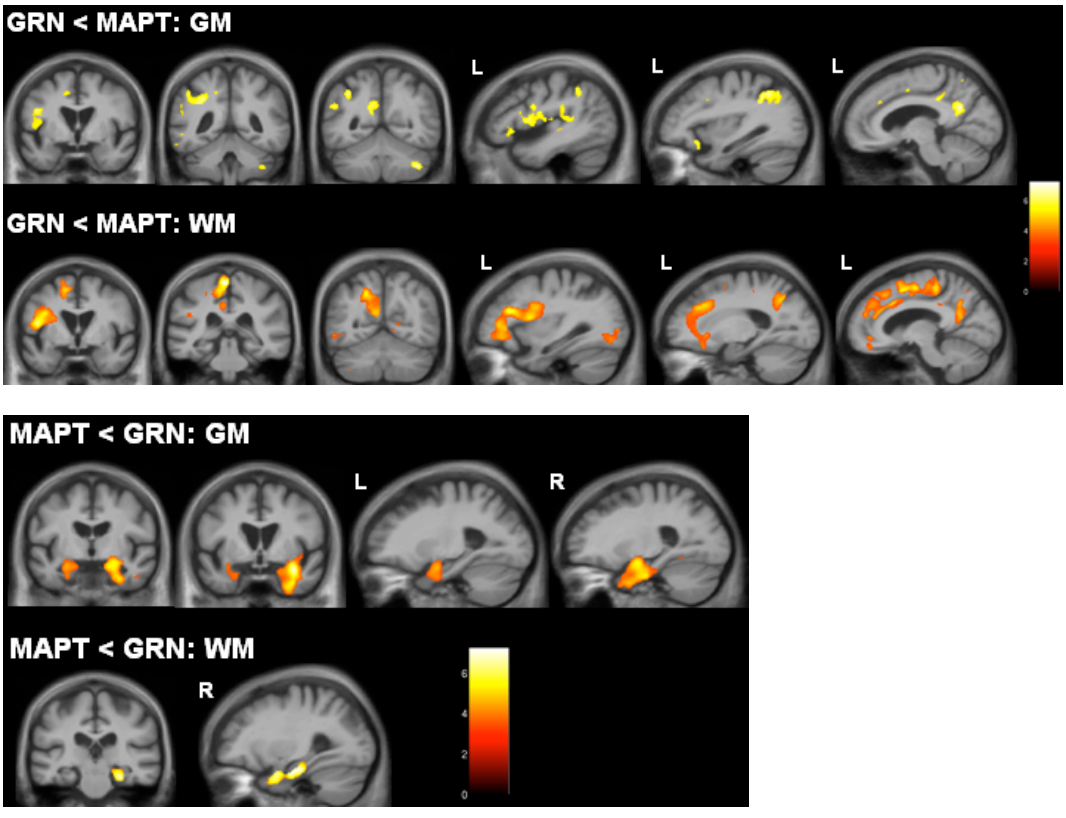
MAPT v GRN group comparisons

Comparing the two mutation groups directly in the flipped VBM analysis (Figure 4.3.6), the GRN group had more marked and asymmetric grey matter loss in inferior frontal lobe [-40, 2, 8], dorsal insula [-36, 8, 3], posterior temporal [-46, -36, 10] and inferior parietal [-34, -55, 37]

lobes and precuneus [-9, -57, 22], and more marked and similarly asymmetric white matter loss in areas likely to be in the superior longitudinal fasciculus [-38, -2, 16] and cingulum [-14, 29, 24]. The MAPT group had more marked grey matter loss in the anterior and medial temporal lobes bilaterally [32, 0, -17; 32, 2, -30; 21, -7, -17; -28, -3, -15] and more prominent involvement of the fornices [28, -13, -21; 27, -22, -18] (Figure 4.3.6).

Figure 4.3.6

VBM analysis comparing grey matter (GM) and white matter (WM) atrophy between *GRN*- and *MAPT*-associated FTLD groups. The top panels show regions where tissue intensity was reduced in the *GRN* group relative to the *MAPT* group (*GRN*<*MAPT*) and bottom panels show regions where tissue intensity was reduced in the *MAPT* group relative to the *GRN* group (*MAPT*<*GRN*). The colour bar (lower right) indicates the t score. Left (L) and right (R) markers are shown for ease of reference however this analysis was performed on flipped images (see text).



DISCUSSION

This study shows that *GRN* and *MAPT* mutation-associated FTLD differ in their underlying clinical, neuropsychological and neuroanatomical patterns. *GRN* patients presented with

bvFTD, PNFA or CBS. No patients with a classic SD syndrome or PSP were found to have mutations. Considering the clinical presentation in more detail, *GRN* patients who present with behavioural symptoms commonly have apathy as the initial presenting feature although most of the common behavioural symptoms of bvFTD are also seen during the disease. Previous case series have described language output impairment as a feature of *GRN* mutations (Cruts et al, 2006; Gass et al, 2006; Snowden et al, 2006; Mesulam et al, 2007; Pickering-Brown et al, 2008). In our study different language phenotypes were seen within the cohort: many patients presenting with bvFTD had decreased spontaneous speech in the absence of speech errors, consistent with dynamic aphasia, often becoming mute as the disease progressed (Snowden et al, 2006; Pickering-Brown et al, 2008). Other patients presented with PNFA, a primary language syndrome known to be heterogeneous in its clinical presentation (Grossman et al, 2004). In contrast, patients with *MAPT* mutations all presented with bvFTD.

Patients with pathogenic *GRN* mutations who had a CBS are described in this series. Some of these patients had an overlap of PNFA and CBS: this is a well-described syndrome overlap (Graham et al, 2003) although the underlying pathology in many previously reported cases has been tau-positive corticobasal degeneration pathology (Knopman et al, 2005). CBS is classically described as involving the frontal and parietal lobes both clinically and radiologically, differing from other FTLD syndromes with its more posterior cerebral involvement. In fact, despite heterogeneity by established clinical criteria, all of the *GRN* patients in this series had evidence of early parietal lobe dysfunction on neuropsychometric testing. This has been noted previously (Spina et al, 2007; Le Ber et al, 2007) and study of this current cohort confirms the involvement of the parietal lobes early in *GRN*-associated FTLD with much lesser involvement in other genetic and clinical subgroups (except in cases of CBS).

Using convergent imaging techniques this study suggests that *GRN* and *MAPT* mutations differentially affect neuronal loss at the level of large-scale cortical networks and their white matter connections. *GRN* mutations preferentially affect an asymmetrical distributed network of frontal, insular, cingulate, parietal and temporal areas linked by intra-hemispheric long association tracts, while *MAPT* mutations preferentially affect a more restricted but bi-

hemispheric network of anteromedial temporal and orbitofrontal areas linked via the fornices and uncinate fasciculi. Disease evolution is more rapid in *GRN*- than *MAPT*-associated FTLD. Moreover, the degree of asymmetry increases over time in the *GRN*- (but not the *MAPT*-) associated cases: in conjunction with the evidence presented here for asymmetric longitudinal intrahemispheric volume loss, this increasing asymmetry implies that the pathological process in *GRN*-associated FTLD is focused within the maximally affected hemisphere. The present findings help to integrate previous evidence concerning anatomical signatures (Whitwell et al, 2005; Whitwell et al, 2007a; Whitwell et al, 2009; Ghetti et al, 2008) and brain size (Josephs et al, 2007) in *GRN* and *MAPT* mutation cases. Further, the findings provide a direct demonstration of mutation-specific abnormalities of white matter circuitry in a head-to-head comparison of these molecular lesions.

White matter involvement in FTLD has been little studied but long association tracts including the anterior cingulum and superior longitudinal fasciculus have been implicated (Seeley et al, 2008; Borroni et al, 2008c). A diffusion tensor imaging study in presymptomatic patients with *GRN* mutations showed left uncinate fasciculus, arcuate fasciculus (part of the superior longitudinal fasciculus), and the left inferior fronto-occipital fasciculus (Borroni et al, 2008c). In the present study, the use of an unbiased technique (VBM) has revealed a cluster of white matter pathways expressing distinct molecular associations, including pathways (such as the fornix) not previously pre-specified in imaging studies of genetic FTLD. It will be important in future studies of genetic FTLD to investigate the complementary information about white matter tracts that can be provided by diffusion tractography.

Neural network dysfunction has been proposed to underpin phenotypic features of neurodegenerative disease including FTLD (Seeley et al, 2009), and in particular, behavioural dysfunction in bvFTD has been ascribed to selective vulnerability within a frontal-insula-anterior cingulate network (Seeley et al, 2006; Seeley et al, 2007; Seeley, 2008; Seeley et al, 2008). This network is affected by both GRN and MAPT mutations, suggesting that it is vulnerable to different pathological processes in FTLD. However, the most significant areas of atrophy here were differentiated according to the underlying molecular abnormality: atrophy in

a ventral orbitofrontal-medial temporal-ventral insula network was associated with *MAPT* mutations and atrophy in a more dorsal and asymmetrical anterior cingulate-dorsal insula-temporal-parietal network was associated with *GRN* mutations. This suggests that large-scale neural network dysfunction is a signature of specific molecular pathologies within the FTLD spectrum. The genetically defined networks identified here are aligned with anatomically similar functional networks delineated in functional connectivity and resting-state network fMRI studies of healthy individuals (Seeley et al, 2009; Damoiseaux et al, 2006; Beckmann et al, 2005; Margulies et al, 2007). Network dysfunction here provides a pathophysiological bridge between molecular dysfunction and the clinical phenotype in different genetically-mediated forms of FTLD: clinically, *MAPT* mutations produce behavioural symptoms (especially disinhibition) and later semantic impairment consistent with involvement of the ventral behavioural-semantic network (Seeley et al, 2009); while *GRN* mutations may produce bvFTD (with early involvement of the dorsal network in the right cerebral hemisphere), progressive aphasia (with early involvement of the dorsal network in the left cerebral hemisphere) or a corticobasal syndrome (with early involvement of more posterior parts of the dorsal network in either hemisphere).

A crucial unsolved question concerns the mechanisms whereby these different molecular lesions produce such strikingly dissimilar patterns of neural network breakdown. There are three interrelated pathophysiological issues here: firstly, how one mutation produces asymmetrical cerebral damage and another more symmetrical damage; secondly, how these distinctive patterns of atrophy are maintained or amplified as the disease evolves; and finally, how phenotypic variation arises such that a particular mutation may selectively damage different cerebral hemispheres even between members of the same family. The variable clinical presentation of genetic FTLD suggests that molecular lesions do not specify a precise initial anatomical locus of brain damage: the initiation of disease in a particular brain region may be a stochastic event or could reflect hemispheric vulnerability due to developmental or other environmental change (Mesulam, 2009). However, the evidence from this study suggests that, once initiated, the pattern of disease evolution and the type of evolution that can occur is constrained by the underlying molecular abnormality. Particular mutations are likely to exert

their effects via the patterns of large-scale network connectivity that exist in the healthy brain, with connectivity between homotopic cortical areas (which is variable in different parts of the brain) being a crucial factor in linking a particular molecular lesion with symmetrical or asymmetrical network involvement (Stark et al, 2008). At a molecular level, *GRN* and *MAPT* are likely to be differently toxic to neurons: loss of *GRN*-mediated trophic support (Eriksen et al, 2008) might particularly disrupt long axonal connections within a hemisphere, whereas in *MAPT*-associated FTLD, toxic gain of function (Gendron et al, 2009) and the effects of diffusible tau with local spread to neighbouring brain regions (Brunden et 2008; Clavaguera et al, 2009) might lead to relatively restricted damage maximally affecting nearby synapses and local interneuronal populations within a functional brain region. The concept of large-scale neural network breakdown linked to specific molecular lesions may be relevant to the pathogenenesis of a number of neurodegenerative pathologies. Further work is required to test these hypotheses and establish the true status of molecular network dysfunction in the pathogenesis of FTLD and indeed, the broader spectrum of neurodegenerative disease.

4.4 Clinico-pathological correlation of language impairment in FTLD

As discussed in Chapter 3.1 the correlation between clinical syndrome of PNFA and SD and the underlying pathology is not one-to-one. Previous studies have identified that SD is mostly due to ubiquitin-positive, TDP-positive pathology (Rossor et al, 2000; Davies et al, 2005; Shi et al, 2005; Snowden et al, 2007a; Hodges et al, 2007) but the more heterogeneous clinical syndrome of PNFA has a wider range of underlying pathologies (Hodges et al, 2004; Shi et al, 2005; Josephs et al, 2006; Snowden et al, 2007a). This section reviews the underlying pathologies in a retrospective cohort of patients with language impairment in FTLD with comparison of neuropsychological and imaging features.

METHODS

A retrospective review of patients with a diagnosis in the FTLD spectrum according to consensus criteria who had attended the Specialist Cognitive Disorders Clinic, Queen Square, London, UK, and who had donated their brains for post-mortem analysis, was performed. 5 patients with a diagnosis of FTLD had also had a brain biopsy during life and were also examined. Of a cohort of 103 patients, 9 had a diagnosis of PNFA, 24 patients had a diagnosis of SD with the other patients having a diagnosis of bvFTD, FTD-MND, CBS or PSP.

All cases had had detailed neuropsychological assessments over the course of the disease. Naming was assessed with the Graded Naming Test or the Oldfield naming test (Oldfield et al, 1965; McKenna et al, 1980) whilst verbal and visual episodic memory were assessed using the Recognition Memory Tests for Words and Faces, respectively (Warrington, 1984) and executive function was assessed using the Weigl test or a Modified Card Sorting test (Weigl, 1948; Nelson, 1976). Other cognitive domains assessed included calculation (Graded Difficulty Arithmetic Test, Jackson et al, 1986) and visuospatial and visuoperceptual skills (subtests of the Visual Object and Spatial Perception (VOSP) battery, Warrington et al, 1991). Patients were recorded as having a deficit in a particular cognitive domain if they scored below the 5th percentile on the relevant test. Only assessments within the first five years from symptom onset were used in order to assess early symptoms.

For the SD cohort, volumetric imaging methods were as described in Chapter 2 with measures of whole brain, hemisphere volume and left/right hemisphere ratio. Cortical thickness estimation was performed as decribed in Chapter 2.

RESULTS

PNFA cohort

Of the 9 cases with a clinical diagnosis of PNFA, 7 had FTLD-tau pathology, 4 with CBD and 3 with Pick's disease, and 2 cases had type 3 FTLD-TDP. 4 of the cases had volumetric MRI imaging (2 with CBD and 2 with Pick's disease) and the cross-sectional imaging patterns in a combined cohort of these 4 cases were investigated in Chapter 3.3. A comparison of the clinical and neuropsychological data on these patients is shown in Table 4.4.1. Neurologically, one of the patients with type 3 TDP pathology had neurophysiological evidence of motor neurone disease with two of the patients with CBS pathology had parkinsonism consistent with a corticobasal syndrome i.e. an asymmetrical akinetic-rigid syndrome with myoclonus and dystonia. There were few behavioural symptoms although some patients developed one of the features seen in the behavioural variant of FTLD i.e. apathy, obsessive behaviour or abnormal eating behaviour although no patients developed disinhibition. All patients had a mild anomia which became worse as the disease progressed with the development of single word comprehension difficulties later in the disorder. Memory was relatively intact in most patients as was visuospatial skills. Executive dysfunction however was seen in most of the patients and dyscalculia was relatively common. Orofacial apraxia was seen in the tau-positive patients but not in the TDP-positive patients.

Table 4.4.1

Clinical and neuropsychological features of pathologically-confirmed PNFA patients within first five years of symptom onset, + = present, - = absent.

Patient	Age at onset	Total duration	MND	Parkinsonism	Apathy	Disinhibition	Obsessive behaviour	Abnormal eating behaviour	Episodic memory impairment	Dyscalculia	Orofacial apraxia	Limb apraxia	Visuospatial impairment	Executive dysfunction
CBD1	61	6.3	-	-	-	-	+	-	+	+	NT	-	-	+
CBD2	65	8.8	-	+ (CBS)	-	-	-	-	-	-	+	+	-	+
CBD3	59	11.6	-	+ (CBS)	-	-	-	+	-	+	+	+	-	+
CBD4	60	10.2	-	-	-	-	-	+	-	-	+	+	-	+
Pick1	57	10.8	-	-	+	-	-	-	-	-	+	-	-	+
Pick2	43	NK	-	-	+	-	-	-	+	+	-	-	-	+
Pick3	50	NK	-	-	-	-	-	-	-	+	+	+	-	-
TDP1	64	5.5	-	-	-	-	-	-	+	+	-	+	+	+
TDP2	62	2.4	+	-	+	-	-	-	+	+	-	-	-	+

SD cohort

Of the 24 patients with a clinical diagnosis of SD, 20 had type 1 FTLD-TDP pathology. The remaining 4 cases all had FTLD-tau Pick's disease pathology. Cross-sectional imaging was available on 14 cases – 11 with type 1 FTLD-TDP pathology and 3 with Pick's disease with longitudinal imaging available in 8 of the FTLD-TDP patients and all 3 of the Pick's disease patients. The cross-sectional imaging patterns of the 11 cases with Type 1 FTLD-TDP were investigated in Chapter 3.3. In this Chapter the imaging (and also the clinical and neuropsychological features) in this group were compared with those with Pick's disease. A third disease group comparison consisted of a further five patients in the post-mortem cohort with FTLD-tau pathology and *MAPT* mutations (four 10+16 mutations and one G389R mutation) who had been previously identified (during review of their neuropsychometry in Chapter 4.3) as having developed semantic impairment during the course of their illness (although with an initial bvFTD syndrome at onset) (Figures 4.4.1, 4.4.2 and Table 4.4.2). 3 of these patients had longitudinal imaging.

Clinical and demographic features

The three pathological groups were approximately matched for gender (64% male in the TDP group, 67% in the Pick's disease group and 60% in the *MAPT* mutation group). Mean age at symptom onset and at death was significantly younger ($p<0.01$) in the *MAPT* mutation group (mean 48.0, standard deviation 6.4) compared with the two groups with a primary SD syndrome (TDP 61.2, 6.4; Pick's disease 55.0, 1.0). Disease duration did not differ significantly between groups although there was a trend to longer disease duration in the FTLD-tau Pick's group (TDP 12.4, 2.9; Pick's disease 14.5, 4.0; *MAPT* mutations 9.4, 2.9).

All patients developed behavioural symptoms during the disease course although these were the presenting features only in the FTLD-tau *MAPT* mutation group. Despite this behavioural features were similar in each group, most commonly disinhibition, obsessiveness and altered eating behaviour (usually, sweet tooth) with apathy being uncommon. Only the *MAPT* mutation group developed associated parkinsonism.

Neuropsychological features

All patients had semantic impairment as defined by single word comprehension deficit with accompanying anomia. On other cognitive testing there was little difference in terms of performance on tests of episodic memory which was usually impaired although with some patients having spared visual memory with impaired verbal memory. However patients with FTLD-tau Pick's disease more commonly had dyscalculia, consistent with left parietal lobe impairment, and patients with *MAPT* mutations more commonly had executive dysfunction.

Neuroimaging features

All three disease groups had smaller mean whole brain volumes than controls but reduced volume of the left compared with the right hemisphere (left/right hemisphere ratio of <1) was present only in the Type 1 FTLD-TDP and Pick's disease groups with relatively symmetrical hemispheric atrophy in the FTLD-tau *MAPT* mutation group (Table 4.4.2; Figure 4.4.1). This difference in hemisphere asymmetry between the groups was maintained with increasing disease duration (Figure 4.4.1): the Pick's disease group had the most asymmetrical atrophy at onset and atrophy became more asymmetrical as the disease progressed. Brain atrophy in the Type 1 FTLD-TDP group also become more asymmetrical over time, however atrophy in the *MAPT* mutation group was relatively symmetrical compared to the other groups and remained symmetrical as the disease progressed (as already shown above in Chapter 4.3). Of note, individually all cases with asymmetrical atrophy and a primary diagnosis of SD had predominant involvement of the left hemisphere.

These features were corroborated by the cortical thickness analysis (Figure 4.4.2 and Table 4.4.2). All three groups showed overlapping involvement of the anterior temporal lobe. However, there were distinct profiles of cortical thinning in each of the groups. The FTLD-TDP type 1 group had asymmetrical, left greater than right, anterior and inferior temporal lobe involvement with lesser involvement of the left orbitofrontal, cingulate and posterior temporal lobe. The Pick's disease group had involvement of similar cortical areas, however frontal and parietal lobe involvement was more marked than in the TDP43 group. The *MAPT* mutation

group had predominant involvement of anterior temporal lobes, however this was more symmetrical than in the other groups and this group also had bilateral involvement of orbitofrontal cortex.

Figure 4.4.1

Left/right hemisphere volume ratio as a function of disease duration: TDP type 1 (black diamonds), Pick's disease (grey triangles), *MAPT* mutations (red squares). The dotted lines represent the upper and lower limit of the control ratio.

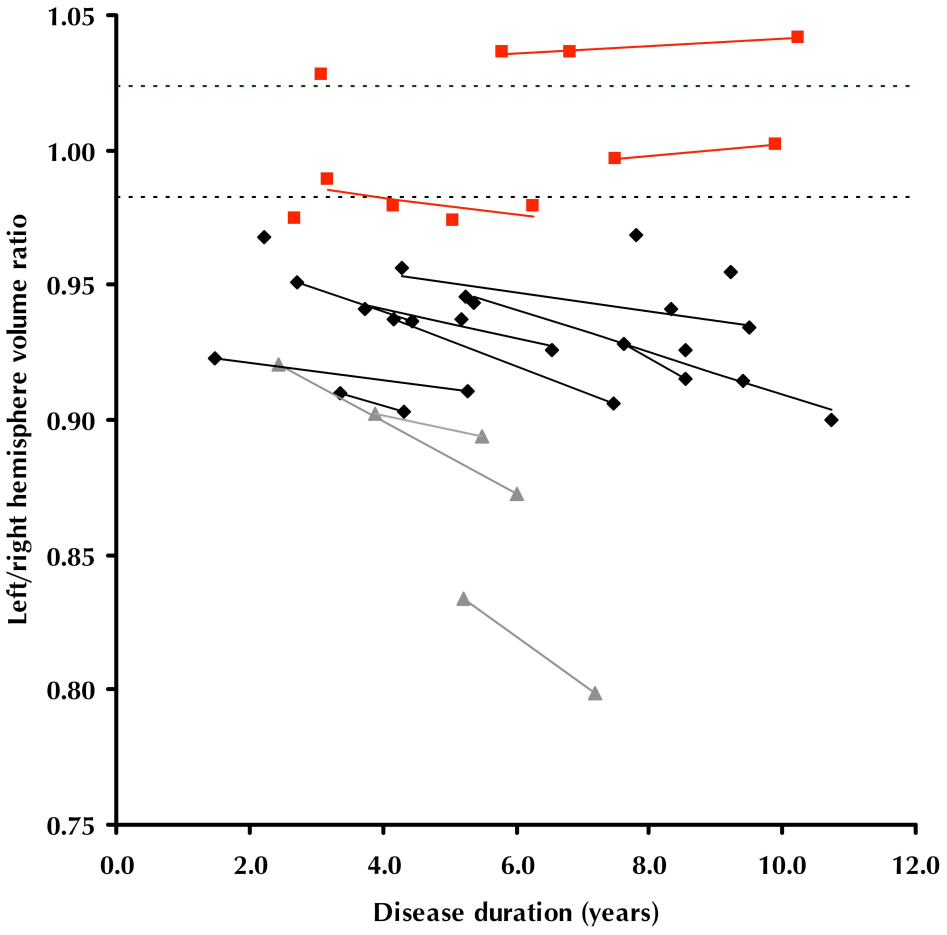


Table 4.4.2

Summary of neuroimaging data: brain volumetry and cortical thickness measures. Mean (standard deviation) values shown.

Imaging parameter	*FTLD-TDP type 1*	*FTLD-tau Pick's disease*	*FTLD-tau MAPT mutations*	*Controls*
Duration at scan (yrs)	4.7 (2.5)	3.8 (1.4)	4.5 (2.1)	N/A
Baseline volume (ml)				
Whole brain	1087.4 (124.9)[a]	1021.5 (130.6)[a]	1137.1 (92.1)	1230.5 (91.6)
Left cerebral hemisphere	521.8 (55.0)[a]	474.3 (72.3)[a, e]	568.9 (39.0)	605.2 (44.0)
Right cerebral hemisphere	553.5 (64.5)[a]	533.7 (55.7)[a]	566.5 (41.4)	605.9 (45.0)
L/R hemisphere volume ratio	0.94 (0.02)[a,c]	0.89 (0.05)[a, d, e]	1.00 (0.03)	1.00 (0.01)
Atrophy rate (%)				
Whole brain BSI	1.8 (0.3)[a]	1.9 (1.1)[a]	1.2 (0.9)[a]	0.3 (0.2)
Cortical thickness (mm)				
Left frontal lobe	2.1 (0.2)	1.7 (0.2)[a, d]	1.9 (0.2)[a]	2.2 (0.2)
Right frontal lobe	2.1 (0.2)	1.7 (0.3)[a, d]	1.9 (0.2)[a, f]	2.2 (0.2)
Left temporal lobe: medial	1.5 (0.2)[a, c]	1.4 (0.4)[a, e]	1.8 (0.3)[a]	2.6 (0.4)
Right temporal lobe: medial	2.0 (0.3)[a]	2.1 (0.3)[a]	1.8 (0.3)[a]	2.6 (0.5)
Left temporal lobe: lateral	1.7 (0.2)[a]	1.6 (0.2)[a]	1.8 (0.2)[a]	2.3 (0.2)
Right temporal lobe: lateral	2.1 (0.2)[a]	1.9 (0.3)[a]	1.9 (0.2)[a]	2.3 (0.2)
Left parietal lobe	1.9 (0.2)	1.6 (0.1)[a, d]	1.8 (0.2)[a]	2.0 (0.2)
Right parietal lobe	2.0 (0.2)	1.8 (0.2)	1.8 (0.2)[a]	2.0 (0.2)

[a]$p<0.05$ disease group significantly worse than controls, [b]$p<0.05$ TDP group significantly smaller than Pick's group, [c]$p<0.05$ TDP group significantly smaller than *MAPT* mutation group, [d]$p<0.05$ Pick's group significantly smaller than TDP group, [e]$p<0.05$ Pick's group significantly smaller than *MAPT* mutation group, [f]$p<0.05$ *MAPT* mutation group significantly smaller than TDP group

Figure 4.4.2

Cortical thickness maps showing patterns of thinning compared with controls, corrected for multiple comparisons at FDR<0.01. Top row: TDP type 1, Pick's disease and *MAPT* mutation groups versus controls; 2nd and 3rd rows, a conjunction analysis looking at the overlap in patterns of thinning between the groups compared with controls.

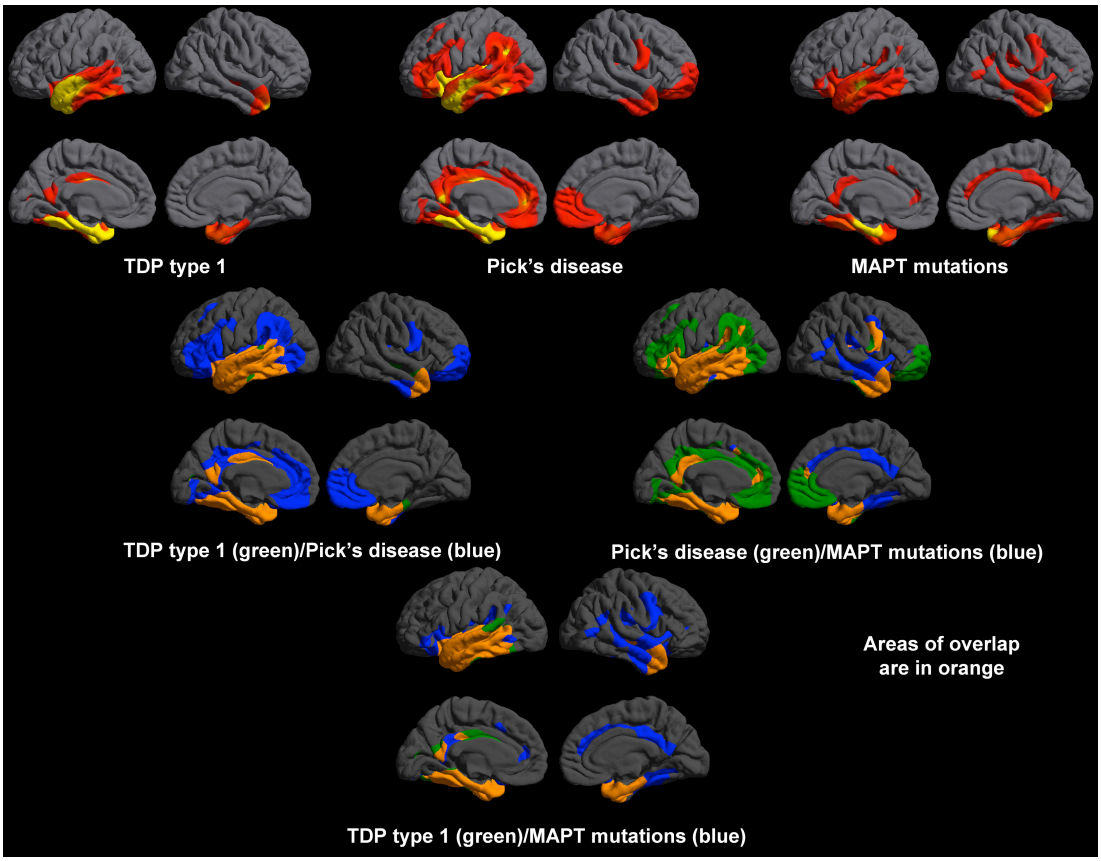


Table 4.4.3

Clinical and neuropsychological features of pathologically-confirmed SD patients and five patients with *MAPT* mutations with semantic impairment, within five years of symptom onset, + = present, - = absent.

Patient	Age at onset	Total duration	Duration at scan	Parkinsonism	Apathy	Disinhibition	Obsessive behaviour	Abnormal eating behaviour	Verbal memory impairment	Visual memory impairment	Dyscalculia	Visuospatial skill impairment	Executive dysfunction
TDP1	59	14.0	4.3	-	-	-	+	+	+	-	-	-	-
TDP2	62	10.8	7.8	-	+	-	-	-	+	+	-	-	-
TDP3	64	14.6	9.2	-	-	+	+	+	+	+	-	-	+
TDP4	55	18.7	5.4	-	-	+	+	-	+	+	-	-	-
TDP5	67	8.7	3.7	-	-	+	+	+	+	-	-	-	-
TDP6	64	10.8	2.2	-	-	-	-	-	+	+	-	-	-
TDP7	69	11.3	1.5	-	-	+	+	-	NT	NT	NT	NT	NT
TDP8	52	9.9	3.4	-	-	+	+	-	+	+	+	-	-
TDP9	50	14.4	7.6	-	-	+	+	-	+	+	-	-	-
TDP10	64	10.3	4.2	-	+	-	+	-	+	+	-	-	-
TDP11	67	12.3	2.7	-	+	-	+	-	+	+	-	-	-
Pick1	55	13.0	2.4	-	-	-	-	-	+	+	+	-	+
Pick2	54	19.0	3.9	-	-	+	+	+	+	-	+	-	-
Pick3	56	11.5	5.2	-	-	+	+	-	+	-	+	-	-
MAPT1	47	13.7	7.5	-	-	+	+	+	+	+	-	-	+
MAPT2	43	6.3	3.1	-	+	+	+	+	+	+	-	-	+
MAPT3	42	10.4	5.8	+	-	+	+	-	+	+	-	-	+
MAPT4	50	8.1	3.2	-	-	+	-	-	+	+	-	-	+
MAPT5	58	8.4	2.7	+	+	+	+	+	+	+	-	-	+

DISCUSSION

This study has investigated the clinico-pathological features of PNFA and SD syndromes. In both syndromes, tau and TDP pathology is seen although in PNFA, tau predominates and in SD, TDP predominates.

PNFA was associated in this study with CBD or Pick's pathology most commonly, particularly when there was orofacial apraxia or a parkinsonian syndrome. The one patient with motor neurone disease had TDP pathology as would be predicted from previous studies although in this case type 3 pathology was seen rather than type 2 pathology which is more commonly associated with FTD-MND. Further studies of the neurolinguistic and neurological features in relation to the neuroanatomical findings in a larger case series will be required to understand the differences between the different pathologies causing a nonfluent aphasia.

Consistent with previous evidence the most common pathological substrate of SD was Type 1 FTLD-TDP: patients in this group had a relatively uniform clinico-anatomical syndrome typical of that previously described in SD, with semantic impairment at presentation and later behavioural symptoms but few other cognitive deficits and relatively circumscribed, asymmetric anteroinferior temporal lobe involvement. The group with FTLD-tau Pick's disease had a broadly similar SD syndrome but with early prominent dyscalculia clinically and more extensive neuroanatomical involvement of the frontal and parietal lobes on neuroimaging and neuropathological analysis. The *MAPT* mutation group presented with bvFTD: this group had involvement of the anterior temporal lobes in common with the other two groups, but this was more symmetrical and there was also substantial orbitofrontal lobe involvement. These findings underline the potential for clinical and anatomical overlap amongst SD-like syndromes within the FTLD spectrum. All three groups here had prominent involvement of the left anterior temporal lobe neuroradiologically, while the extent of right anterior temporal lobe involvement was more variable: the consistent involvement of the left anterior temporal lobe supports a core role for this region in the pathogenesis of verbal semantic impairment (Hodges et al, 2007), which was a defining clinical feature of all cases in this study. The timing of onset of behavioural symptoms varied between the three groups here, however similar behavioural

features emerged in all groups during the disease course. These features, most notably disinhibition, obsessive behaviour and abnormal eating behaviour, are consistent with the present neuroimaging findings: together, the behavioural and anatomical findings suggest involvement of a common orbitofrontal-insular-striatal network (Liu et al, 2004; Woolley et al, 2007). Early bilateral involvement of this network in patients with *MAPT* mutations would account for the prominent behavioural changes and associated parkinsonism in this group.

Several caveats need to be considered when interpreting the present findings. Opportunities for anatomical and pathological correlation are limited, and case numbers in this (as in previous) series are small. The study was retrospective; accordingly, nonverbal semantic and other neuropsychological functions could not be systematically assessed. Furthermore, cortical regions beyond the temporal lobe are increasingly involved as SD evolves (as shown in Chapter 3.3), implying that anatomical differentiation may be clearer early in the course. Taking these caveats into account, this study supports a core syndrome of semantic impairment and left anterior temporal lobe damage which defines typical SD in association with FTLD-TDP type 1 pathology, and a spectrum of less common 'halo' cases with additional clinical manifestations, distinct patterns of (extra-temporal) tissue damage and histopathological features of tauopathy.

Chapter 4 summary

This Chapter provides new information about the underlying genetics and pathology of language impairment in FTLD. The initial study in Chapter 4.2 shows as hypothesized that SD and PNFA can be familial although much less than bvFTD. SD is the less familial of the two syndromes and no mutations in the known genes that cause FTLD were found. PNFA can be familial in some instances and often due to mutations in the progranulin gene. Importantly, mutations in this gene, discovered only recently as causing FTLD, are the first gene mutations shown to cause a primary progressive aphasia. Pathogenic mutations in the *MAPT* gene do not seem to cause a primary progressive aphasia (usually presenting with bvFTD) but can cause semantic memory impairment later in the disease. Comparison of the neuroanatomy of this group with *GRN* mutations in Chapter 4.3 shows a more symmetrical atrophy pattern predominantly affecting anterior and medial temporal lobes, overlapping with the classical pattern of atrophy seen in SD. In Chapter 4.4 this comparison is shown with pathologically-confirmed SD patients showing the overlap but differences between *MAPT* mutations and SD caused by TDP pathology or tau-positive Pick's disease pathology. Chapter 4.3 shows that *GRN* mutations appear to cause a relatively distinct clinico-anatomical phenotype with markedly asymmetrical atrophy that extends back to involve the parietal lobes relatively early. In this sense the term frontotemporal lobar degeneration does not fully account for the features seen in *GRN* mutation-associated neurodegenerative disease. Chapter 4.4 shows that both PNFA and SD can be associated with tau-positive and TDP-43-positive pathology although PNFA is more commonly associated with tau-positive pathology and SD is predominantly associated with TDP-43-positive pathology. Preliminary study of the neuroanatomy of different SD clinico-pathological syndromes in Chapter 4.4 suggests that the groups may be distinguished by the extent to which frontal and parietal lobes are affected early on in the disease (early parietal lobe involvement more likely with Pick's disease than TDP pathology in these cases).

5. Heterogeneity of the nonfluent progressive aphasia variants

Chapter 3 investigated the imaging features of the two canonical subtypes of PPA, namely SD and PNFA. However more recent work has attempted to refine the classification of PPA with several papers describing a third, essentially nonfluent, subtype, known as the logopenic/phonological variant of PPA (LPA) (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008; Wilson et al, 2009b). Less commonly, other progressive aphasia phenotypes have also been described such as progressive anomia or non-fluent anomic aphasia (Snowden et al, 2003; Snowden et al, 2007b; Pickering-Brown et al, 2008), progressive mixed aphasia (Grossman et al, 2004; Alladi et al, 2007) and phonological buffer disorder (Kartsounis et al, 2007). This clinical syndromic heterogeneity is also matched by the pathological and genetic heterogeneity of PPA as described in Chapter 4: post-mortem series have shown both tau-positive and ubiquitin-positive, TDP-43 positive FTLD pathology as well as Alzheimer disease (AD) pathology (Galton et al, 2000; Hodges et al, 2004; Josephs et al, 2006; Snowden et al, 2007a; Mesulam et al, 2008), whilst genetically, *GRN* mutations can cause PPA (Snowden et al, 2006; Snowden et al, 2007b; Mesulam et al, 2007). This chapter aims to explore the heterogeneity of the nonfluent progressive aphasia variants by examining a prospective series of 33 patients with PPA. Following a review of the literature (5.1) this chapter investigates the clinical, neuropsychological and imaging features in this group particularly in the 24 patients with a "nonfluent aphasia" (i.e. excluding 9 patients with a diagnosis of SD) (5.2 and 5.3). Subsets of this larger group are investigated in more detail in the three other sections of this chapter: PPA associated with progranulin mutations (5.4), Alzheimer pathology (5.5) and atypical parkinsonian disorders (5.6).

The specific hypotheses of Chapter 5 are:

1. There are multiple clinical subtypes of the nonfluent progressive aphasias that can be split based on the presence of agrammatism and apraxia of speech.
2. More specific clinical subtypes will map onto more well-defined genetic and pathological causes.

3. Progranulin-associated primary progressive aphasia will be associated with a nonfluent form that has other features such as parietal lobe involvement.
4. Nonfluent aphasias associated with apraxia of speech will be associated with the atypical parkinsonian disorders, corticobasal syndrome and progressive supranuclear palsy.

5.1 Overview of previous studies

The best described of the non-PNFA, non-SD phenotypes is logopenic or logopenic/phonological aphasia (LPA). Although initially reported in early descriptions of PPA (Mesulam, 1982; Mesulam 2001; Kertesz, 2003), it was first described in detail by Gorno-Tempini and colleagues in 2004 (Gorno-Tempini et al, 2004a) and then expanded upon by the same group in a series of follow-up studies (Rosen et al, 2006; Amici et al, 2006; Gorno-Tempini et al, 2008; Rabinovici et al, 2008; Brambati et al, 2009a; Wilson et al, 2009b). The disorder has been characterized as a primary phonological loop deficit resulting in impaired verbal short term (phonological) memory, impaired sentence repetition and comprehension with sparse spontaneous speech and frequent prolonged word-finding pauses. The most significantly atrophied areas in LPA are the left posterior superior temporal and inferior parietal lobes and to a lesser extent posterior cingulate and middle/inferior temporal lobe disease, although the extent to which atrophy spreads beyond these areas has been unclear (Gorno-Tempini et al, 2008; Rabinovici et al, 2008; Wilson et al, 2009b). Small post-mortem and amyloid imaging studies have emphasized an association of LPA with AD pathology (Mesulam et al, 2008; Rabinovici et al, 2008) and this is consistent with the literature on atypical language variants of AD (Galton et al, 2000; Croot et al, 2000; Alladi et al, 2007; Stopford et al, 2007; Stopford et al, 2008) in which the phenotype described in many cases is similar to the LPA syndrome. With this said, the clinico-pathological correlation is not straightforward as AD pathology has also been associated (albeit less commonly) with other PPA phenotypes (Knibb et al, 2006; Gerstner et al, 2007; Rabinovici et al, 2008; Pereira et al, 2009). Pathologically-confirmed imaging studies of this group are limited although one retrospective study of patients with progressive aphasia and AD pathology, some of whom would have fit proposed criteria for LPA, showed left temporo-parietal lobe atrophy, similar to to the previous clinical studies (Josephs et al, 2008b).

Aphasia associated with *GRN* mutations has been little studied. Early descriptions suggested that these patients had a "nonfluent aphasia" (Baker et al, 2006; Cruts et al, 2006; Snowden et al, 2006; Mesulam et al, 2007; Pickering-Brown et al, 2008; Cruchaga et al, 2008) although one detailed case study has described progressive anomia without motor speech impairment

and subsequent development of repetition and reading deficits (Snowden et al, 2003; Snowden et al, 2007b). General neuroimaging features of patients with *GRN* mutations have been described in Chapter 4 however there have been few studies purely looking at patients with PPA and *GRN* mutations.

There are a number of other speech and language syndromes that have been described that do not clearly fit into the current scheme of the progressive aphasias. As none of these has any described pathological or genetic associations, it remains unclear exactly how they are related to SD, PNFA or LPA. Some progressive articulatory disorders associated with cortical disease have been described as "progressive dysarthria" (Soliveri et al, 2003), "slowly progressive anarthria" (Broussolle et al, 1996; Lucchelli et al, 2005) and "pure progressive aphemia" (Cohen et al, 1993). Whilst it is clear that dysarthria commonly occurs as an accompaniment to apraxia of speech and aphasia in PNFA (Gorno-Tempini et al, 2004a; Ogar et al, 2007), it remains unclear whether isolated "cortical dysarthrias" eventually progress into the same syndrome, or whether they remain isolated (and if so, what the pathological cause is). Similarly, progressive impairment of prosody is also described both in isolation (Ghacibeh et al, 2003; Luzzi et al, 2008), and as part of PPA syndromes (Tsao et al, 2004). A further "aphasia" is that of so-called "dynamic aphasia", a disorder of verbal planning which has been described as a progressive disorder independent of a widespread apathy or abulia (Warren et al, 2003).

5.2 Neuropsychological studies of PPA subtypes

As described above, the nonfluent variants of PPA seem to be more heterogeneous than SD. This heterogeneity is in both the clinical and neuropsychological features as well as the genetic and pathological associations. This study of a prospective cohort of patients with PPA was designed to investigate such heterogeneity.

METHODS

33 consecutive patients with a progressive language disorder as the leading feature at presentation (a diagnosis of PPA according to current criteria: Mesulam, 2001; Mesulam, 2003) and not fulfilling criteria for an alternative dementia syndrome were recruited to the study. All patients initially had a structured clinical history and neurological examination. Based on this initial assessment and independent of any brain imaging findings, nine patients were diagnosed with SD (Neary et al, 1998; Adlam et al, 2006). The remaining 24 patients had nonfluent speech: these patients are the main focus of this study. 18 cognitively-normal control subjects matched for gender and age also participated. All patients and controls underwent a neurological examination: this was normal in all but three patients, one of whom had a corticobasal syndrome (asymmetrical akinetic-rigid syndrome with limb apraxia and dystonia) and two who had a progressive supranuclear palsy syndrome (axial rigidity with a supranuclear gaze palsy). Genetic screening for mutations in *GRN* and *MAPT* was performed in all patients: three patients were found to have mutations in *GRN* with all other patients negative for either *GRN* or *MAPT* mutations. Examination of cerebrospinal fluid had been undertaken in nine patients as part of their initial clinical assessment: this revealed a CSF profile of total tau/Aβ42 levels consistent with AD in five cases (i.e. high total tau and low Aβ42: Hulstaert et al, 1999).

Spontaneous speech analysis

The initial step in the study was to analyze the spontaneous speech of the patients. This was performed in order to classify the patients into groups according to the presence or absence of agrammatism and apraxia of speech (AOS). These features were chosen because they have been considered in previous studies (and also previously defined criteria) to be the primary causes of speech impairment in the nonfluent aphasias (Neary et al, 1998; Gorno-Tempini et

al, 2004a; Josephs et al, 2006). As described in Chapter 2 a sample of spontaneous speech was obtained by asking all of the subjects to talk about their last holiday and to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination (Goodglass et al, 1983). Examples from four of the patients are given below (Figure 5.2.1).

Figure 5.2.1

Examples of spontaneous speech from nonfluent aphasic patients (total time in seconds for which the patients spoke in each example is given in parentheses, speech production errors are italicized)

Patient 1

- The washing up… the *spilding*… the sink… and the children… is is… getting on the chair… on the stool and the… flowing over sink… over… wiping up… (58s)
- Last holiday… Christmas time… it was the last holiday we had taken… we end up getting the last holiday… by car… by coach… the holiday is the … (76s)

Patient 2

- On the left hand side… two children are… are… trying to get to the… cookie jar the… daughter is holding her hand up to receive a cookie while her b… brother has climbed up on a stool to reach the cookie jar… the lid is open but the poor boy is about to fall… d… down because the three-legged stool is about to… overturn… a fitted kitchen with c… cupboards under and over (60s)
- Together with my wife we flew to Prague and stayed in the Paris hotel which is an ar… ar…art deco styled hotel… we walked in the ancient square and were sur… prised to see and hear that there were or…ches… tras playing classical music… we thoroughly enjoyed our four days in Prague and then flew on to visit our son in Warsaw… Poland… we had been there before but it was nice to… to see his family and we *fleb* flew back to England re..refreshed and *exho..lorated* by the experience (62s)

Patient 3

- Not so good… and this thing's gone down… and it's gone the wrong way… on that way… and this woman is fall down… there to lose this… and that's about it really (22s)
- Well, we've been to France… we've got a place now in France at the end… which is very good… we were there for a week… first thing in the morning… that's all I think really… we got the *trine*… the top thing (55s)

Patient 4

- We went to America and I can't remember whereabouts in there … and that was in… that was this year… no… last holiday… America… by plane… in the city… we went into a city… we stayed… further on… then we… cause we knew somebody… that was there… so that's where we stopped… with them (65s)
- Somebody is going to fall off… with a cookie jar… and he's going to fall off and his sister is trying to find *ik*… get his… one of those cookies to give her… and then the water's all over there… because it's just you know… they didn't turn the tap off and she's looking there but she doesn't realize that she's got all this water coming down there (50s)

The samples were recorded and subsequently transcribed and analysed for:

a. Number of agrammatic (morphological or syntactic) errors made per minute, and
b. Presence or absence of apraxia of speech defined as a motor speech disorder with the features of hesitancy, effortfulness with articulatory groping, phonetic errors and dysprosody (Croot, 2002; Ogar et al, 2005) – all of these features were required to be present for AOS to be defined as being present.

Speech was also analyzed for a number of further measures including:

1) Number of words produced per minute
2) Number of speech production errors produced per minute. However, because of difficulties in reliably classifying speech production errors as phonemic (errors in the selection of speech sounds to be executed) versus phonetic or apraxic (errors in the execution of a programmed speech sound) these were not analyzed separately.
3) Word-finding pauses: the distribution of inter-word intervals in the speech sample was analysed using a customised routine running under Matlab® which measured intervals between vocalisations (both within and between sentences).
4) Patients who have difficulty finding words often use more high frequency (common) words and less low frequency (less common) words and so the mean frequency rating of the nouns used by patients in speech was investigated. Frequency ratings were based on the CELEX database (Baayen et al, 1993) with scores converted to a mean log score as word frequencies from this scale varied between 10 and 100,000.

From this initial spontaneous speech analysis four groups of patients were identified: those with AOS with and without agrammatism, and those without AOS with and without agrammatism: these are shown in Table 5.2.1 as well as the other spontaneous speech data and compared to the cognitively-normal control group and the disease-control group of SD patients (for whom spontaneous speech data was available in 8 out of 9 patients, mean (standard deviation) disease duration of 5.0 (1.1) years) using linear regression models within STATA 10.0.

Table 5.2.1

General demographic and spontaneous speech data (AOS = apraxia of speech, Agramm = agrammatism. Examples given in Figure 5.2.1 correspond with AOS with agrammatism (Patient 1), AOS with no agrammatism (Patient 2), no AOS with agrammatism (Patient 3), no AOS and no agrammatism (Patient 4). *p<0.05 disease group worse than controls)

Test	Controls	SD	AOS		No AOS	
			Agramm	No agramm	Agramm	No agramm
Number of patients	18	8	10	4	3	7
Age	67.9 (5.4)	57.6 (9.4)	69.0 (5.6)	78.5 (4.4)	62.0 (8.6)	65.2 (6.4)
Gender (M:F)	9:9	3:5	8:2	2:2	2:1	4:3
Agrammatic errors/min	0.0 (0.0)	0.0 (0.0)	3.7 (0.9)*	0.0 (0.0)	2.7 (0.7)*	0.0 (0.0)
Speech rate (words/min)	133.9 (22.9)	127.5 (26.6)	30.8 (15.1)*	49.5 (21.9)*	44.9 (14.4)*	63.1 (19.5)*
Speech production errors/min	0.0 (0.0)	0.0 (0.0)	1.9 (1.7)*	0.2 (0.2)	0.9 (0.1)*	0.3 (0.4)
Mean pause length (s)	1.0 (0.2)	1.0 (0.1)	1.5 (0.3)*	1.3 (0.2)*	1.9 (0.3)*	1.5 (0.3)*
Frequency rating of nouns used (log score)	1.8 (0.1)	2.1 (0.2)*	1.9 (0.2)	1.9 (0.2)	2.4 (0.3)*	2.0 (0.2)*
Frequency rating of verbs used (log score)	2.4 (0.2)	2.6 (0.3)	2.9 (0.2)*	2.6 (0.2)	3.0 (0.0)*	2.9 (0.2)*

- Both groups with AOS had reduced speech rate and increased mean pause length compared with controls and made speech production errors. The range of noun use (noun frequency) was similar to controls. However, the group with agrammatism had significantly more speech production errors and a trend to lower speech rate and longer mean pause duration than the group without agrammatism. Furthermore, there was a higher mean verb but not noun frequency than controls in the *AOS/agrammatism* group suggesting a tendency to use more common verbs (the reverse pattern to the SD group).
- Patients with *no AOS/agrammatism* differed from the *AOS/agrammatism* group in having a significantly longer mean pause length and a higher mean frequency of nouns used (i.e. a tendency to use more common nouns, similar to the SD group) although they also had a higher mean frequency of verbs used than controls.
- The *no AOS/no agrammatism* group had reduced speech rate, occasional speech production errors and longer mean pause duration compared both with controls and SD; similar to the *no AOS/agrammatism* group, there was a higher mean noun and verb frequency.

Disease duration and disease severity

One of the problems of comparing patients with PPA cross-sectionally is that within a single study patients will be at a variety of different stages of the disease. This is compounded by the fact that the different clinico-pathological syndromes are likely to progress at different rates between syndromes and also for a given syndrome in different patients. We therefore initially compared disease duration from first symptom onset with disease severity as measured by both the Mini-Mental State Examination (Folstein et al, 1975) and the Clinical Dementia Rating (Morris, 1993) sum-of-boxes (Table 5.2.2). Although patients within each group had decreasing MMSE and increasing CDR-sum-of-boxes with increased disease duration, for the same disease duration patients without AOS had a lower MMSE and higher CDR-sum of boxes, and therefore could be classified as "more severe" on this basis.

Table 5.2.2

Disease severity data

Test	Controls	AOS		No AOS	
		Agrammatism	No agrammatism	Agrammatism	No agrammatism
Disease duration (yrs)	N/A	6.1 (1.7)	3.3 (1.6)	4.3 (0.5)	4.4 (1.1)
MMSE (/30)	29.7 (0.8)	24.0 (5.4)*	25.3 (6.9)	13.7 (8.4)*	15.9 (5.8)*
CDR-sum of boxes	0.0 (0.0)	3.0 (1.5)*	1.4 (0.9)*	4.5 (1.3)*	4.6 (1.1)*

*p<0.05 disease group worse than controls

With these four groups defined, all of the patients went on to have further neuropsychological testing including the specifically designed battery of neurolinguistic tests discussed in Chapter 2. Patients were also assessed on tests of executive function (Nonverbal fluency task from the D-KEFS executive function battery (Delis et al, 2001), episodic memory (Camden Pictorial Recognition Memory Test, Warrington, 1996), visuoperceptual skills (the Object Decision subtest of the Visual Object and Space Perception Battery, VOSP, Warrington, 1991). Limb apraxia was noted as part of the structured neurological examination.

Disease severity (MMSE) was adjusted for in subsequent statistical analyses comparing disease groups. Using STATA 10.0 linear regression models were used to compare performance on neuropsychological tests between groups (95% bootstrap confidence intervals with 1000 replicates). Wilcoxon signed-rank tests were used for within disease group comparisons.

RESULTS (Table 5.2.3)

Naming and single word comprehension

The AOS with agrammatism group and two groups without AOS were significantly anomic compared to controls with a trend to greater anomia in the groups without AOS compared to those with AOS. A similar pattern was seen on tests of noun comprehension although verb comprehension was only significantly worse than controls in the no AOS/agrammatism group

(with a trend to better performance on nouns compared to verbs in this group). Word-picture matching was significantly worse than controls in all groups apart from the AOS/no agrammatism group with significantly worse performance in the no AOS/agrammatism group compared to the AOS groups.

Verbal short-term memory, sentence comprehension and grammar

Compared with controls, all groups apart from the AOS/no agrammatism group had decreased digit span with significantly lower digit span in the agrammatism-only group compared with the two groups with AOS. Performance on the modified PALPA55 subtest was impaired in all groups compared with controls. The AOS/agrammatism group performed significantly worse on comprehension of passive reversible than active non-reversible sentences ($p=0.01$, suggesting a true grammatical comprehension deficit). The no AOS/agrammatism performed poorly on all sentences but there was a trend to better performance on the passive reversible sentences compared to active non-reversible sentences ($p=0.10$). The no AOS/no agrammatism group performed similarly on all sentences and did not benefit from the effect of non-reversibility in simpler active sentences. Verb tense comprehension was affected similarly in all groups apart from the AOS/no agrammatism group who performed normally.

Speech repetition

The AOS/agrammatism and the two groups without AOS performed worse than controls on all tests although the AOS/no agrammatism group performed worse than controls only on the nonword and cliché repetition tasks. The no AOS/no agrammatism group performed significantly worse on sentence repetition compared to cliché, nonword or word repetition with a similar trend in the no AOS/agrammatism group but no significant differences between words and sentences in the AOS groups.

Reading and spelling

Word and nonword reading was impaired in all groups although most significantly in the no AOS/agrammatism group. Irregular word reading was also most affected in the no

AOS/agrammatism group. Spelling was significantly worse than controls in all groups apart from the AOS/no agrammatism group.

Other cognitive domains

Executive function was impaired in all but the AOS/no agrammatism group who did not show impaired function relative to controls on any of the tests. Episodic memory was impaired relative to controls only in the no AOS/no agrammatism group. Limb apraxia was present in all patients in the two groups without AOS but only in 70% of the AOS with agrammatism and 25% of the AOS without agrammatism.

Table 5.2.3

Neurolinguistic and neuropsychological data

Test	Controls	AOS		No AOS	
		Agramm	No agramm	Agramm	No agramm
NAMING AND SINGLE WORD COMPREHENSION					
Graded Naming Test (/30)	25.2 (2.2)	9.1 (8.5)*	16.0 (11.0)	1.3 (2.3)*,c,d	1.5 (1.8)*,f,g
Simple naming test (/20)	19.7 (0.7)	12.1 (6.5)*	14.3 (7.0)	2.3 (4.0)*,c,d	5.1 (4.2)*,f,g
Noun synonyms (/25)	24.3 (0.8)	19.6 (2.4)*	22.5 (2.6)	15.7 (4.6)*,d	16.6 (1.6)*,f,g
Verb synonyms (/25)	23.2 (1.6)	20.1 (4.3)	22.0 (3.6)	12.0 (2.6)*,c,d,e	19.0 (3.5)
Word-picture matching (/30)	28.3 (0.9)	24.7 (4.4)*	27.3 (2.2)	16.6 (5.6)*,c,d	21.1 (2.7)*,f,g
VERBAL SHORT-TERM MEMORY, SENTENCE COMPREHENSION AND GRAMMAR					
Digit span forwards	6.9 (0.6)	4.9 (1.4)*	5.5 (1.7)	2.0 (1.0)*,c,d	4.0 (1.8)*
PALPA 55 (modified version) – total (/24)	23.4 (0.8)	18.4 (4.4)*,a	22.0 (1.2)*	13.3 (5.5)*,d	13.3 (6.3)*,g
Passive reversible (%)	97.9 (4.8)	66.4 (32.3)*	87.5 (14.4)	45.8 (19.1)*,d	41.1 (28.6)*,g
Passive non-reversible (%)	95.8 (9.6)	75.0 (26.4)*	87.7 (14.4)	58.3 (28.9)*	60.7 (31.8)*
Active reversible (%)	99.3 (2.9)	81.4 (20.6)*	93.8 (7.2)	54.2 (26.0)*,d	64.3 (33.4)*,g
Active non-reversible (%)	95.8 (9.6)	90.0 (12.9)	100.0 (0.0)	75.0 (25.0)	60.7 (24.4)*,f,g
Verb tense comprehension test (/20)	19.8 (0.4)	16.5 (3.5)*,a	19.5 (0.6)	15.0 (3.6)*,d	14.9 (2.7)*,g
SPEECH REPETITION					
Single word repetition (% correct)	100.0 (0.0)	63.8 (39.8)*,a	98.8 (1.6)	48.9 (14.6)*,d,e	85.2 (17.7)*
Nonword repetition (% correct)	100.0 (0.0)	57.0 (37.9)*	73.8 (22.1)*	45.0 (20.0)*,e	79.3 (19.9)*
Cliché repetition (% correct)	100.0 (0.0)	53.0 (44.7)*,a	93.3 (5.8)*	6.7 (11.5)*,c,d,e	61.4 (44.1)*
Novel sentence repetition (% correct)	100.0 (0.0)	56.0 (44.8)*,a	100.0 (0.0)	3.3 (5.8)*,c,d,e	45.7 (41.2)*,g
READING AND SPELLING					
Schonell Reading Test (% correct)	99.2 (1.6)	61.1 (29.8)*	84.5 (16.6)*	17.7 (27.2)*,c,d,e	73.7 (14.7)*
Irregular word reading test (% correct)	94.3 (5.6)	51.3 (27.5)*,a	83.3 (18.3)	8.9 (7.7)*,c,d,e	44.8 (22.0)*,g
Graded Difficulty Nonword Reading Test (% correct)	98.6 (3.3)	40.0 (31.9)*	68.8 (30.1)*	23.3 (32.1)*	42.5 (36.2)*

Graded Difficulty Spelling Test (/30)	26.0 (2.7)	11.9 (10.4)*	18.3 (13.3)	1.0 (1.7)*[c,d]	5.8 (5.6)*
OTHER COGNITIVE DOMAINS					
D-KEFS Nonverbal Fluency (scaled score)	10.7 (3.0)	6.3 (2.6)*	8.0 (2.4)	5.0 (3.6)*	3.7 (1.8)*[f,g]
Camden Topographical Memory Test (/30)	29.7 (0.8)	29.3 (0.8)	29.8 (0.5)	25.3 (8.1)	25.3 (4.2)*[f,g]
VOSP Object decision subtest (/20)	17.5 (2.3)	16.8 (2.4)[b]	15.3 (3.2)	18.7 (0.6)	16.0 (2.4)[h]
ABA-2 subtest 3A limb praxis (/50)	49.9 (0.2)	41.9 (11.7)*	43.8 (9.0)	28.0 (16.6)*	39.8 (6.9)*

*p<0.05 disease group worse than controls , [a]p<0.05 AOS/agrammatism worse than AOS/no agrammatism, [b]p<0.05 AOS/agrammatism worse than No AOS/agrammatism, [c]p<0.05 No AOS/agrammatism worse than AOS/agrammatism, [d]p<0.05 No AOS/agrammatism worse than AOS/no agrammatism, [e]p<0.05 No AOS/agrammatism worse than No AOS/no agrammatism, [f]p<0.05 No AOS/no agrammatism worse than AOS/agrammatism [g]p<0.05 No AOS/no agrammatism worse than AOS/no agrammatism [h]p<0.05 No AOS/no agrammatism worse than No AOS/agrammatism.

Summary of findings in each group

AOS/agrammatism

This group had reduced speech rate with speech production errors and increased pause length with nonfluency due to the dual deficits of AOS and agrammatism. These features distinguished the speech of these patients from the SD group, with in addition reduced verb but normal noun frequency (completing a double dissociation with SD). Other key features were anomia, impaired sentence comprehension (particularly for more complex sentences), impaired speech repetition that was similarly severe for both words and sentences, impaired reading (particularly nonwords), and in addition executive dysfunction and limb apraxia. There was also evidence of a mild single word comprehension deficit, particularly in more severely affected patients. This profile is consistent with previous descriptions of PNFA. Of note, the three patients with parkinsonism all fell within this group.

AOS/no agrammatism

This group had shorter mean disease duration than the AOS/agrammatism group and showed a trend towards a qualitatively similar though less severe profile of deficits. Mean speech rate was reduced and pause length prolonged in relation to both healthy controls and the SD group.

Despite the absence of expressive agrammatism, this group performed significantly worse than controls on the PALPA55 sentence comprehension test (suggesting a deficit of receptive grammar). These patients also had mild dyslexia (affecting nonwords). These features suggest that this "pure AOS" group may represent an earlier stage of PNFA prior to development of expressive agrammatism, though this remains unresolved in the absence of longitudinal data.

No AOS/agrammatism

These patients were more severely affected than the two groups with AOS (based on MMSE and CDR scores) with impairments on most linguistic tests. However, speech rate and speech production errors were similar to the groups with AOS. In addition, visual object perception and episodic memory were preserved, indicating a pre-eminently aphasic syndrome. The most notable linguistic problems were profound anomia, impaired single word comprehension (particularly verbs), severely reduced digit span (phonological short term memory deficit), impaired sentence comprehension and repetition, and severe dyslexia. Expressive agrammatism was found on formal speech analysis but difficult to assess at the bedside because of the slow speech rate and word-finding pauses. This group comprised the patients with *GRN* mutations.

No AOS/no agrammatism

The most prominent features in this group were anomia, decreased forward digit span, impaired sentence comprehension (both simple and complex), impaired sentence repetition with relatively spared single word repetition, dyslexia (particularly for nonwords) and relatively intact single word comprehension. These features are consistent with current descriptive criteria for LPA. In addition (and in comparison to the no AOS / agrammatism subgroup), these patients had extra-linguistic deficits of episodic memory, and object decision). Of note, most patients in this group had CSF biomarkers consistent with AD pathology.

DISCUSSION

Four distinct syndromic groups within a cohort of patients with non-fluent PPA are described in this study. The groups were delineated using an initial classification from spontaneous speech

based on the presence or absence of AOS and expressive agrammatism and subsequent detailed linguistic analysis. These groups comprised an AOS only group, an AOS plus agrammatism group, an agrammatism only group and a group without AOS or agrammatism. The AOS groups together constitute the majority of patients with what is probably best described as PNFA or PNFA/AOS. It remains unclear whether the AOS group without agrammatism represent a less severe form of PNFA, consistent with the observation that agrammatism may supervene later in the course of progressive AOS, or whether 'pure AOS' constitutes a pathophysiologically distinct group within the PPA spectrum. The group without AOS or agrammatism has a syndrome equivalent to LPA as described by other research groups (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008): this syndrome is likely to be underpinned by AD pathology in a high proportion of cases, consistent with the CSF data here. The agrammatism-only group is more problematic: while the presence of agrammatism would tend to align such cases with PNFA this syndrome has some linguistic and neuropsychological similarity to LPA (including long word-finding pauses, a severe phonological verbal short memory deficit, impaired sentence processing and non-linguistic dominant parietal lobe features). All patients in this group here had *GRN* mutations, suggesting that *GRN* mutations may lead to a distinct aphasia syndrome albeit overlapping PNFA/AOS and LPA. If indeed agrammatism is a defining feature of *GRN*-associated PPA, this supports recent work suggesting that TDP-43 pathology may be a substrate for agrammatic PPA (Deramecourt et al, 2010), though this group may include both cases with *GRN* mutations and other patients lacking such mutations. More fine-grained analyses of expressive agrammatism in PPA may allow further clinically meaningful subdivisions of this potentially broad category (e.g., an association with tau pathology, Mesulam et al, 2008; Knibb et al, 2009).

This study underlines the importance of an initial clinical assessment of the patient's spontaneous speech, and in particular the presence or absence of AOS and agrammatism, in classifying non-fluent PPA syndromes at presentation. However, this is not to imply that clinical characterisation of PPA syndromes is straightforward: analysis of spontaneous speech may be difficult where this is severely impoverished. It is likely that a particular syndrome will change in character as disease evolves: disease duration and severity therefore need to be

taken into account. Moreover, there is a need for new operational and clinical measures of PPA that can characterise positively the *no AOS/no agrammatism* group defined 'negatively' here, and potentially, other less common PPA syndromes not captured by the simple classification scheme presented here. This category might, for example, encompass the controversial entity of 'cortical anarthria' (Kertesz et al, 2003).

This study further illustrates that a number of standard neuropsychological measures are of limited use in differentiating PPA syndromes. However, within particular cognitive domains, certain features may allow more detailed neuropsychological stratification of these syndromes. Consistent with previous work (Rhee et al, 2001; Gorno-Tempini et al, 2004a; Grossman et al, 2005; Gorno-Tempini et al, 2008; Peelle et al, 2007) this study indicates sentence comprehension deficits may occur in the nonfluent PPA spectrum. The LPA (*no AOS/no agrammatism*) group here exhibited more severe deficits of sentence syntax and verb tense processing than the groups with AOS, and in contrast to the patients with AOS, showed impaired processing of both simple (active) and complex (passive) sentences with limited sensitivity to non-reversibility (a semantic cue based on agency). Considering the PPA spectrum as a whole, various deficits may potentially contribute to impaired sentence processing, including impaired verbal working memory as well as primary grammatical or semantic deficits (Fiebach et al, 2001; Friederici e tal, 2002). These potential mechanisms of impaired sentence comprehension remain to be elucidated fully.

The different syndromes have distinct patterns of speech repetition that may help to distinguish them. Previous studies have suggested that patients with LPA have significantly worse performance on sentences compared to single words (Gorno-Tempini et al, 2008) and this pattern was also seen in the LPA (*no AOS/no agrammatism*) group here. A similar but more severe dichotomy between single word and sentence repetition was seen in the *GRN* (*no AOS/agrammatism*) group. In comparison to these groups without AOS, the *AOS/agrammatism* group performed similarly on words, nonwords, clichés and sentences while the *AOS/no agrammatism* group showed deficits of nonword and cliché repetition.

Our findings further highlight dyslexia and dysgraphia as key components of the nonfluent PPA variants: performance on nonwords was worse for both the AOS groups and the LPA (*no AOS/no agrammatism*) group, in keeping with a phonological dyslexia (Brambati et al, 2009). In the *GRN* (*no AOS/agrammatism*) group reading of all word types was affected, suggesting a more severe dyslexia. Cognitive domains beyond language may provide further information: episodic memory impairment (on the relatively easy test used here) was a consistent feature only of the LPA (*no AOS/no agrammatism*) group.

This study has the limitations of small case numbers, absence of a longitudinal arm to track the evolution of deficits, and lack of pathological correlation. This study has focused on a relatively small number of neurolinguistic measures with clear clinical relevance. More fine-grained psycholinguistic analyses (for example, to characterise motor speech deficits, and intra- versus inter-sentential pauses) may further refine the distinction between PPA subgroups. These caveats notwithstanding, the findings provide a rationale for future studies of the nosology of PPA syndromes. It is likely that there are at least three nonfluent PPA syndromes and that these are distinct rather than variations on a single continuum (Knibb et al, 2009; Deramecourt et al, 2010). The PNFA/AOS syndrome can be associated with a corticobasal or progressive supranuclear palsy syndrome during life (Josephs et al, 2006) and based on previous evidence is most commonly underpinned by tau pathology, while the LPA syndrome without AOS or agrammatism is closely associated with AD pathology, and *GRN*-associated aphasia has TDP-43 pathology. The phenotype of *GRN*-associated aphasia is of neurobiological interest since it is associated with a specific molecular dysfunction. Though detailed neuropsychological studies are few, previous reports include descriptions of a syndrome of progressive "non-fluent anomic aphasia' (Snowden et al, 2007): clearly, additional unidentified factors are likely to influence the particular phenotype of GRN aphasia, and it is not suggested that there is a precise correspondence between GRN mutations and the *no AOS/agrammatism* aphasia syndrome delineated here. The *GRN*-aphasia syndrome may bear some neuropsychological and neuroanatomical similarity to LPA, however there are certain key points of distinction. While detection of expressive agrammatism may be difficult at the bedside, for the reasons outlined above, our findings suggest that additional neurolinguistic features may help

discriminate this *GRN*-associated aphasia syndrome from cases of LPA (e.g., impaired single word comprehension). It is unlikely that the *GRN*-associated *no AOS/agrammatism* group simply represents a more severe syndrome than LPA: both groups without AOS here had very similar disease durations and disease severity as indexed by MMSE and CDR. Detailed neuropsychological evaluation may be required to differentiate the *GRN*-associated and AD-associated syndromes and this could in turn potentially help guide investigation of patients with PPA. Systematic, hypothesis-led longitudinal neurolinguistic analyses with neuroanatomical, genetic and pathological correlation in larger patient cohorts will be important directions for future work.

5.3 Imaging of PPA subtypes

Chapter 5.2 investigated the neurolinguistic and cognitive features of nonfluent aphasias. The evidence from this seems to show that there are at least three different nonfluent disease groups: PNFA (both groups with AOS), LPA (no AOS/no agrammatism) and *GRN*-PPA (no AOS/agrammatism). However, Chapter 5.2 did not investigate the neuroanatomical differences between these groups. Hence the patients studied above went on to have structural MR imaging with the complementary techniques of volumetric measurement, cortical thickness analysis and voxel-based morphometry used in this Chapter to investigate the neuroanatomical features of the nonfluent variants in comparison to the control group and the patients with SD.

METHODS

Brain image acquisition is as described in Chapter 2 with volumetric measures as described in Chapter 2 apart from volumetric analysis of specific subcortical structures (hippocampus, amygdala, caudate and brainstem) which were performed using the Freesurfer image analysis suite version 4.0.3 (http://surfer.nmr.mgh.harvard.edu/) (Fischl et al, 2002). For volumetric measures, the groups were compared statistically by looking at the two-tailed contrasts between the group means using a linear regression model in STATA 10.0. Cortical thickness methods are as described in Chapter 2. In this study, cortical thickness was modelled as a function of group, controlling for age, gender and total intracranial volume by including them as nuisance covariates. Contrasts of interest between the estimates of the group parameters were assessed using two-tailed t-tests. Maps showing statistically significant differences between each disease group and healthy controls were generated and corrected for multiple comparisons to control the False Discovery Rate (FDR) at a 0.001 significance level. Voxel-based morphometry was performed as described in Chapter 2. In this study, voxel intensity was modelled as a function of group, and subject age, gender and total intracranial volume were included as nuisance covariates. Separate analyses were performed on the grey and white matter segments. Maps showing single-tailed statistically significant differences between the groups were generated, correcting for multiple comparisons in the disease group-control comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.05 significance level. Statistical parametric maps were displayed as overlays on a study-

specific template, created by warping all native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

RESULTS

Volumetric analysis

All PPA groups had asymmetrical predominantly left-sided cerebral atrophy i.e. mean left/right hemisphere ratio less than one in each group (Table 5.3.1). However, hemispheric asymmetry was most marked in the *GRN*-PPA group (being significantly more asymmetric than all other disease groups). LPA was similar to the SD group in terms of asymmetry (left/right hemisphere ratio=0.94) and significantly more asymmetric than PNFA.

Subcortical volumetric data showed smaller caudate volumes bilaterally in the PNFA group compared to controls (with a trend to smaller brainstem volume also) In the LPA group, the left caudate, hippocampus and amygdala were significantly smaller than controls while only the left hippocampus was significantly smaller in the *GRN*-PPA subgroup. The SD group had smaller left hippocampal and bilateral amygdalae volumes in compared to controls.

Table 5.3.1

Volumetric data for whole brain, left and right cerebral hemisphere, caudate, hippocampus and amygdala volumes as a percentage of total intracranial volume (TIV)

Cerebral region volumes (as a percentage of TIV) *Mean (standard deviation)*	**SD**	**PNFA**	***GRN*-PPA**	**LPA**	**Controls**
Number of subjects	9	14	2	7	18
Whole brain	68.1(3.8)	64.2 (5.7)[a,d]	63.2 (0.8)	65.6 (6.4)	70.1 (4.0)
Left hemisphere	32.7 (2.0)	31.1 (2.9)[a]	28.3 (0.2)[a]	31. (3.1)[a]	34.4 (1.9)
Right hemisphere	34.7 (1.8)	32.2 (2.8)[a,d]	33.9 (0.3)	33.5 (3.2)	34.6 (2.0)
Left/right hemispheric ratio	0.94 (0.01)[a,b]	0.97 (0.04)[a]	0.83 (0.00)[a]	0.94 (0.02)[a]	1.00 (0.01)
Brainstem	1.26 (0.11)	1.20 (0.15)	1.21 (0.07)	1.23 (0.03)	1.27 (0.10)
Left caudate	0.20 (0.03)	0.19 (0.03)[a]	0.19 (0.01)	0.19 (0.02)[a]	0.22 (0.03)
Right caudate	0.22 (0.03)	0.20 (0.02)[a]	0.24 (0.01)	0.21 (0.03)	0.23 (0.04)
Left hippocampus	0.13 (0.04)[a,b,c]	0.20 (0.03)	0.15 (0.02)[a]	0.18 (0.02)[a]	0.22 (0.03)
Right hippocampus	0.21 (0.03)	0.22 (0.03)	0.21 (0.00)	0.22 (0.02)	0.24 (0.03)
Left amygdala	0.04 (0.02)[a,b,c]	0.08 (0.01)	0.07 (0.02)	0.07 (0.02)[a]	0.08 (0.01)
Right amygdala	0.07 (0.02)[a,b,c]	0.08 (0.01)	0.11 (0.00)	0.08 (0.03)	0.09 (0.01)

Statistically significant differences between the groups are represented by superscript letters: [a]$p<0.05$ disease group significantly worse than controls, [b]$p<0.05$ SD worse than PNFA, [c]$p<0.05$ SD worse than LPA, [d]$p<0.05$ PNFA worse than SD.

Cortical thickness analysis

Compared with healthy controls, cortical thinning was predominantly left-sided in all groups (Figure 5.3.1, Table 5.3.2).

Table 5.3.2

Cortical thickness data for the frontal, temporal and parietal lobes

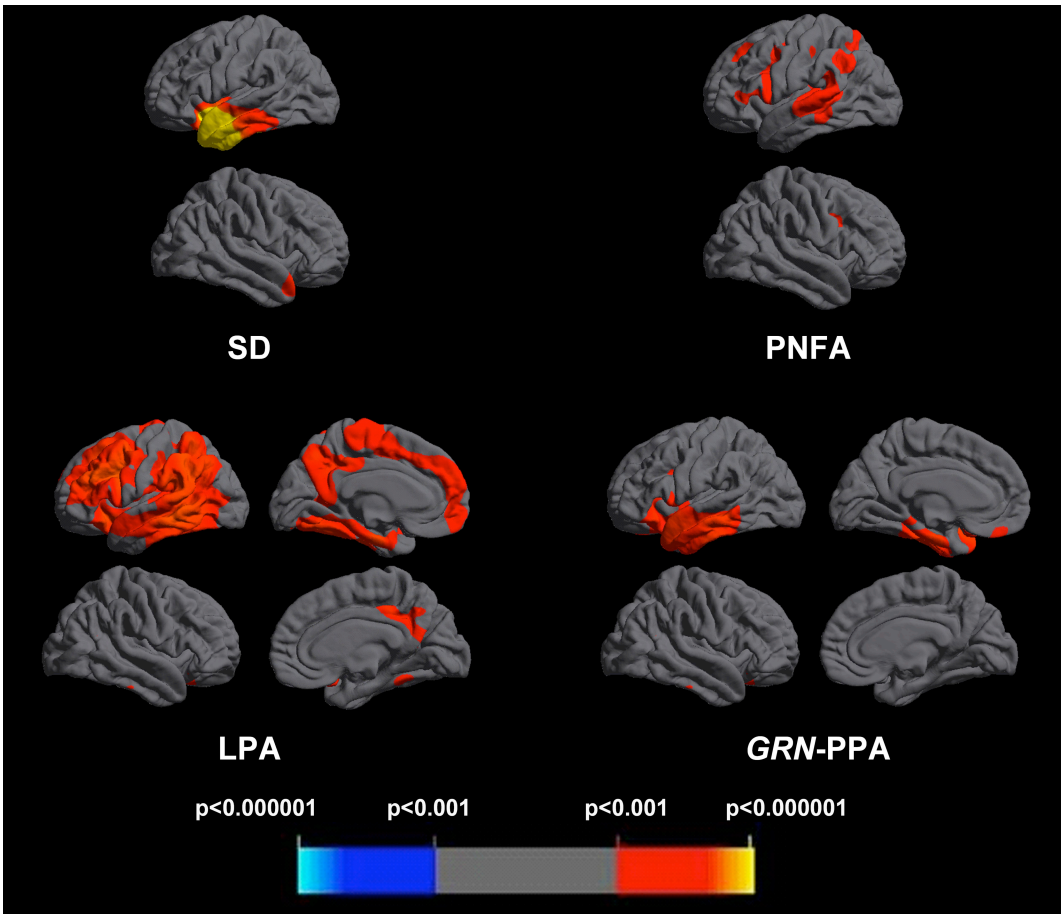
Cortical thickness in each lobe (mm) *Mean (standard deviation)*		SD	PNFA	GRN-PPA	LPA	Controls
Frontal	**Left**	2.2 (0.1)	2.0 (0.2)[a,d]	1.9 (0.1)[a]	2.0 (0.1)[a]	2.2 (0.1)
	Right	2.3 (0.1)	2.1 (0.1)[a,d]	2.3 (0.0)	2.1 (0.1)[a]	2.2 (0.1)
Temporal	**Left**	1.7 (0.2) [a,b]	2.1 (0.3)[a]	1.6 (0.4)[a]	1.9 (0.1)[a]	2.4 (0.1)
	Right	2.2 (0.2)[a]	2.2 (0.2)[a]	2.5 (0.1)	2.2 (0.1)[a]	2.4 (0.1)
Parietal	**Left**	2.0 (0.1)	1.8 (0.2)[a,d]	1.8 (0.1)[a]	1.7 (0.1)[a]	2.0 (0.1)
	Right	2.1 (0.1)	1.9 (0.2)[a,d]	2.2 (0.1)	1.9 (0.1)[a]	2.0 (0.1)

Statistically significant differences between the SD, PNFA, LPA and control groups are represented by superscript letters: [a]$p<0.05$ disease group significantly worse than controls, [b]$p<0.05$ SD worse than PNFA, [c]$p<0.05$ SD worse than LPA.

In the PNFA group there was maximal involvement of the left inferior frontal (pars triangularis and pars opercularis), superior frontal, insular and superior temporal cortex with lesser involvement of the anterior parietal lobe. The LPA and *GRN*-PPA groups revealed overlapping but distinct patterns compared to controls: both groups had mid to posterior temporal lobe and inferior frontal involvement but in the LPA group there was greater temporo-parietal junction and frontal atrophy and in the *GRN*-PPA group there was more anterior temporal atrophy (Figure 5.3.1). As shown previously, the SD group showed involvement of the antero-inferior temporal lobes (left greater than right and particularly the temporal pole, parahippocampal and entorhinal cortex) and to a lesser extent the left frontal lobe (particularly orbitofrontal cortex).

Figure 5.3.1

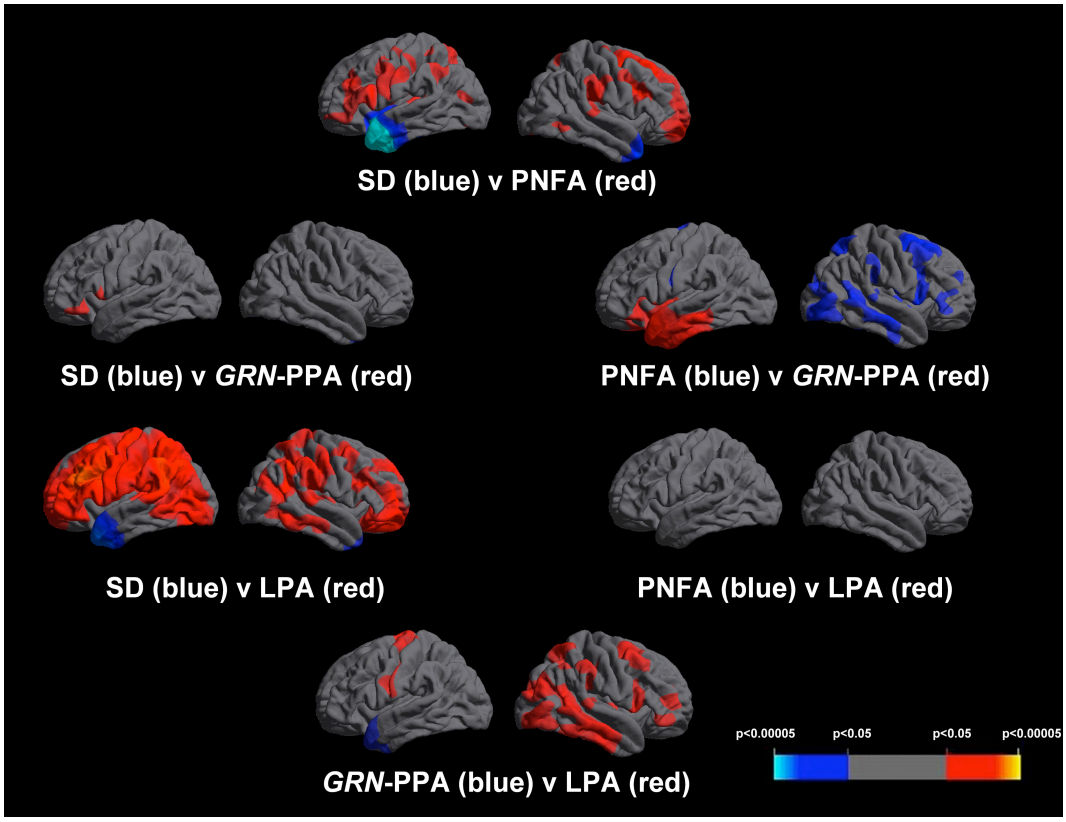
Cortical thickness maps showing patterns of cortical thinning in disease groups compared to healthy controls. For each disease panel, left hemisphere sections are shown above and right hemisphere sections below. Maps are thresholded at p<0.001 after FDR correction over the whole brain volume. The coloured bar represents FDR corrected p-values.



Comparing the disease groups there were no differences at the statistical level of p<0.001 FDR corrected but at less stringent level of p<0.05 FDR corrected there were differences between the groups. The LPA group had more marked thinning of left anterior parietal cortex and extensive cortical areas in the right cerebral hemisphere than the *GRN*-PPA group, while the *GRN*-PPA group had more marked thinning of left anterior temporal cortex than the LPA group (Figure 5.3.2).

Figure 5.3.2

Cortical thickness maps showing patterns of cortical thinning in between disease-group differences. For each disease panel, left hemisphere sections are shown on the left and right hemisphere sections on the right. Maps are thresholded at p<0.05 after FDR correction over the whole brain volume. The coloured bar represents FDR corrected p-values.

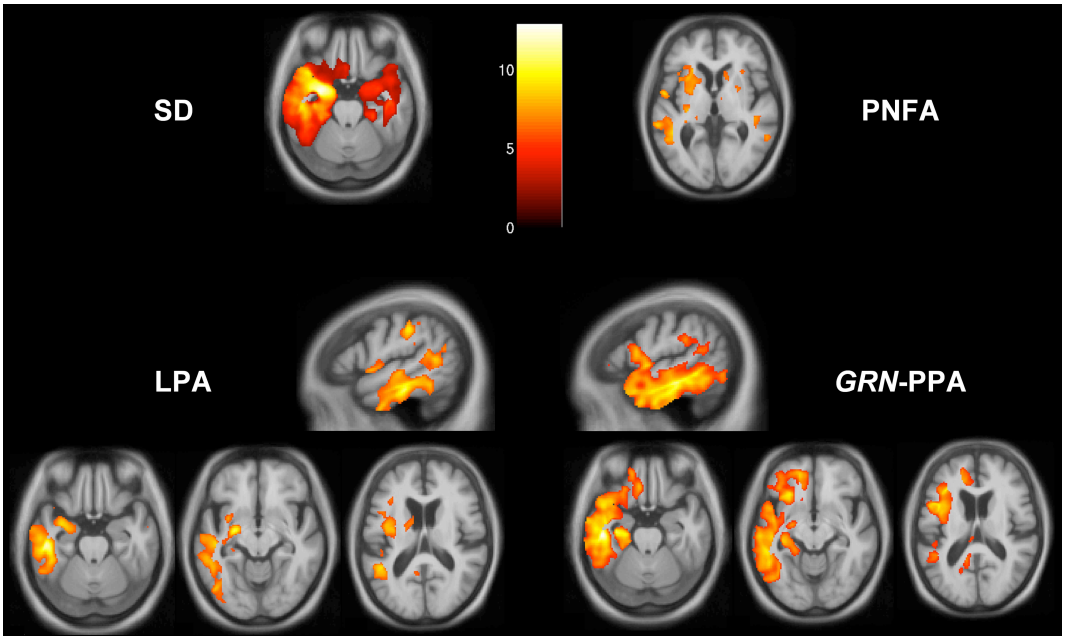


VBM analysis

The VBM analysis corroborated the findings of the cortical thickness analysis with similar findings in the SD and PNFA groups compared to controls (Figure 5.3.3). Patterns of grey matter atrophy overlapped in the LPA and *GRN*-PPA groups, but the LPA group had greater posterior (particularly parietal) [-47, -47, -13; -46, -53, 6] involvement while the *GRN*-PPA group had greater anterior temporal lobe [-43, 3, -31] involvement (Figure 5.3.3). The findings differed from the cortical thickness measures in showing greater overlap between the LPA and *GRN*-PPA groups in posterior temporal, inferior parietal and inferior frontal lobe areas.

Figure 5.3.3

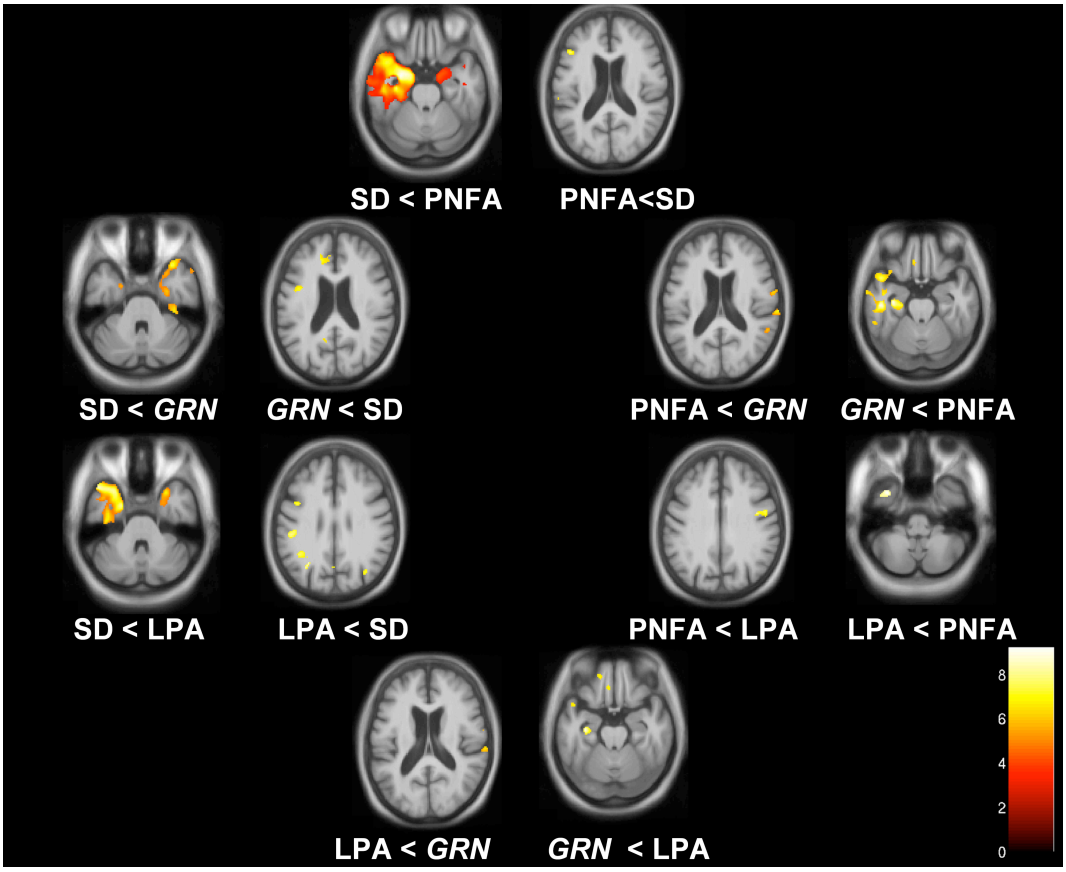
VBM analysis on grey matter regions in PPA groups relative to healthy controls. For each axial section, the left hemisphere is shown on the left; sagittal sections are through the left hemisphere. Maps are thresholded at p<0.05 after FDR correction over the whole brain volume. Grey matter differences are colour coded (red-yellow) in terms of t-score as indicated on the colour bar (right).



Comparing the disease groups there were no significant differences following FDR correction. Comparison at less stringent statistical level of p<0.001 showed some differences between disease groups. The LPA group had greater parietal [-36, -51, 35] and inferior frontal [-36, 0, 21] atrophy than the SD group, and greater left inferior temporal [-43, -22, -25] involvement than the PNFA group; whilst the *GRN*-PPA group had greater inferior frontal [-38, 24, 12] and precuneus [-10, -54, 18] involvement than the SD group, and greater temporal lobe [-45, -21, -21; -32, -18, -17] involvement than the PNFA group (Figure 5.3.4). Compared to the *GRN*-PPA group, the LPA group had greater atrophy in biparietal [37, -28, 46; -26, -21, 58] and right posterior temporal [63, -28, 11] cortices, while the *GRN*-PPA group had greater atrophy of left anterior temporal [-49, 12, -22] and inferior temporal [-34, -18, -30] and left orbitofrontal cortex [-13, 42, -13] than the LPA group (Figure 5.3.4).

Figure 5.3.4

VBM analysis on grey matter regions in disease group comparisons. For each axial section, the left hemisphere is shown on the left. Maps are thresholded at p<0.001 uncorrected. Grey matter differences are colour coded (red-yellow) in terms of t-score as indicated on the colour bar (lower right).

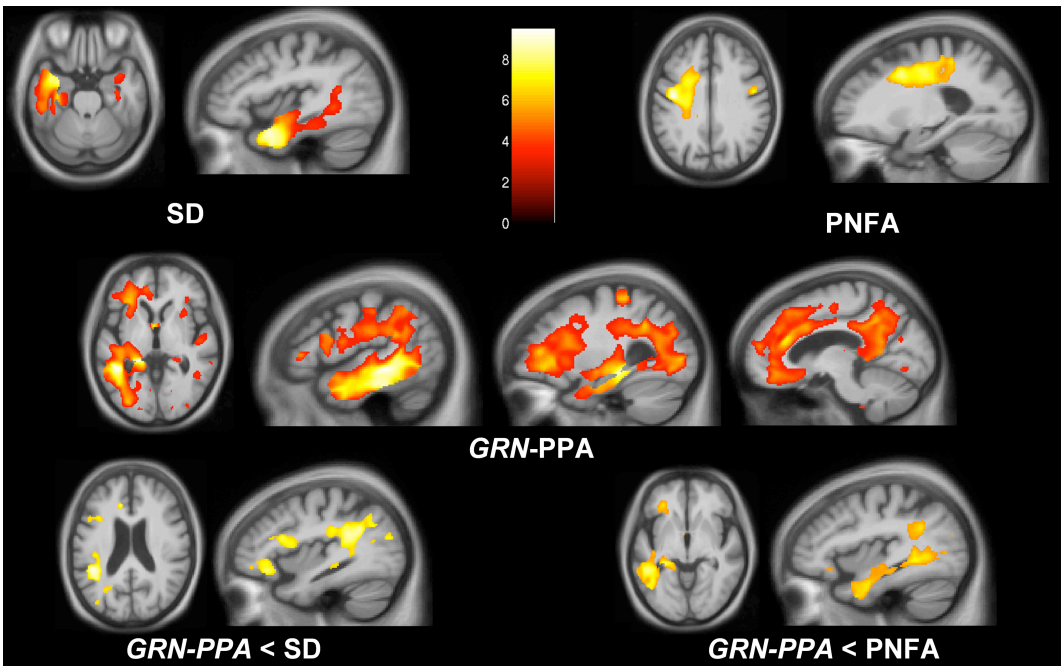


The white matter analysis revealed distinct patterns of tract involvement in each of the three groups: in the SD group, there was involvement of white matter tracts predominantly in the left temporal lobe including the fornix [-26, -36, -8], inferior longitudinal fasciculus [-62, -28, -18] and uncinate fasciculus [-34, 1, -24] (Figure 5.3.5); in the PNFA group, there was maximal involvement of a left frontal lobe white matter region [-39, -10, 31] likely to represent part of the superior longitudinal fasciculus (Figure 5.3.5); and in the *GRN*-PPA group there was most marked involvement of intrahemispheric long association tracts including inferior longitudinal fasciculus [-49, -36, -16], superior longitudinal fasciculus [-38, 9, 12], inferior fronto-occipital fasciculus [-19, -40, -5] and cingulum [-11, 31, 15], and also involvement of the corpus callosum and brainstem tracts. The *GRN* group showed greater involvement of dorsal fronto-parietal tracts [-39, -45, 18] than the SD group, greater involvement of temporal lobe tracts [-

44, -24, -18; -44, -4, -22] than the PNFA group, and greater involvement of both fronto-parietal [-33, 19, 16; -33, -45, 19] and temporal lobe tracts [-44, -24, -18; -44, -4, -22] than the LPA group. The LPA group had no significant white matter involvement relative to either healthy controls or the disease subgroups.

Figure 5.3.5

VBM analysis on white matter regions in PPA subgroups relative to healthy controls. For each axial section, the left hemisphere is shown on the left; sagittal sections are through the left hemisphere. For control comparisons, maps are thresholded at p<0.05 after FDR correction over the whole brain volume; for disease group comparisons, maps are thresholded at p<0.001 uncorrected. White matter differences are colour coded (red-yellow) in terms of t-score as indicated on the colour bar (right).The LPA subgroup showed no significant areas of white matter loss relative to other disease groups at the prescribed threshold.



DISCUSSION

Allowing for the different modalities used and the limited spatial resolution of smoothed data which preclude fine-grained anatomical correlation, complementary volumetric, cortical thickness and morphometric techniques here have shown a broadly convergent pattern of findings. Although there is overlap between LPA and *GRN*-PPA, there are distinct patterns of

atrophy with more posterior temporo-parietal junction and frontal lobe involvement in LPA and more anterior temporal lobe involvement in *GRN*-PPA. These neuroanatomical findings are consistent with differences in the neuropsychological profiles of these two groups shown in Chapter 5.2. Cortical atrophy in the LPA group here appears more extensive than previously reported (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008): this may have been a correlate of relatively more severe disease in the group studied here. However, interpretation of severity effects is problematic where severity measures are closely correlated with the specific effects of the disease process: clues that severity is not the entire explanation for the extensive left hemispheric damage in the LPA group are the somewhat shorter mean disease duration and asymmetry of anatomical damage, suggesting that the disease process in these cases preferentially affects a distributed left hemisphere network.

The findings in these prospectively studied SD and PNFA groups corroborate the work of previous studies as well as that described in Chapter 3, and provide further information about the integrity of white matter pathways that are likely to be critical in binding cortical areas into distributed networks that mediate particular language functions (Scott et al, 2003; Spitsyna et al, 2006; Awad et al, 2007; Seeley et al, 2009). In SD there was asymmetrical, left greater than right anterior temporal lobe atrophy with less marked involvement of orbitofrontal cortex (Galton et al, 2001; Rosen et al, 2002a). In PNFA there was left inferior frontal lobe, insula and superior temporal lobe atrophy with less marked involvement of the caudate and anterior parietal lobe (Nestor et al, 2003; Gorno-Tempini et al, 2004a; Ogar et al, 2007). White matter disease has been little studied in SD and PNFA, however one diffusion tensor imaging study in a mixed "temporal variant" FTLD cohort (Borroni et al, 2007) showed involvement of white matter tracts, including inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, callosal and superior longitudinal fasciculus. The present study with stratification of PPA subgroups is consistent both with previous neuroanatomical findings and with the distinctive neuropsychological profiles of SD and PNFA. In SD, there was predominant involvement of anterior temporal cortices and white matter tracts (fornix, inferior longitudinal fasciculus and uncinate fasciculus) implicated in semantic processing (Spitsyna et al, 2006); while in PNFA, there was predominant involvement of inferior frontal, insular and parieto-temporal cortices

and dorsal white matter tracts (including the superior longitudinal fasciculus) implicated in speech production (Scott et al, 2003).

LPA is defined by the presence of a primary language disorder with the key constellation of impoverished though non-effortful spontaneous speech marred by prominent word-finding pauses and less prominent phonemic errors, anomia, impaired sentence comprehension and impaired repetition particularly of sentences (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008). This language disorder is associated with reduced digit span (indicative of a phonological store deficit). Although a primary defect of phonological working memory has been proposed in LPA (Gorno-Tempini et al, 2008), it is unlikely that the primary cognitive defect in this degenerative syndrome is restricted to a single information processing module. For example, anomia and word-finding pauses might reflect a primary word retrieval deficit or a more specific phonological access deficit linked to disruption of inferior parietal or posterior superior temporal lobe areas, while limb apraxia is likely to reflect involvement of a distinct network mediating the control of voluntary action that includes the left parietal lobe. The pattern of deficits in LPA suggests involvement of the left parieto-temporal junction and functional connections in the dorsal language processing stream linking to inferior frontal areas (Awad et al, 2007; Wong et al, 2009). This pattern is likely to be relatively specific for LPA: a similar pattern has emerged in previous neuroanatomical studies of the syndrome (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008), and furthermore, direct comparison with SD and PNFA cases here revealed distinct group-specific patterns of atrophy.

The finding that the majority of the LPA cases had CSF biomarkers in keeping with AD pathology is consistent with a previous study in which 64% (7/11 cases) of patients with LPA had AD pathology: most of the other cases had FTLD-U pathology, though further genetic analysis was not undertaken (Mesulam et al, 2008). If LPA signals an atypical language presentation of AD in a high proportion of cases, it is noteworthy that the pattern of anatomical changes delineated here could be interpreted as a highly asymmetrical variant of the anatomical profile described in typical amnestic AD, with involvement of the medial temporal lobe, temporo-parietal junction and precuneus (Scahill et al, 2002). Indeed, language

dysfunction and parietal signs frequently develop in the course of typical amnestic AD (Croot et al, 2000; Harasty et al, 2001; Taler et al, 2008b) and an atypical language variant of AD has been described, of which many cases appear to have had an LPA syndrome (Galton et al, 2000; Alladi et al, 2007).

In this study, two patients had *GRN* mutations, which have been shown previously to be associated with asymmetrical hemispheric cortical atrophy frequently involving the parietal lobe (Le Ber et al, 2008; Whitwell et al, 2009). The neuroimaging signature of *GRN*-PPA was strikingly asymmetric, with more severe anterior temporal lobe involvement (and more severe white matter involvement) than with LPA. This neuroanatomical correlate implicates the ventral language processing pathway linking the posterior superior temporal lobe with more anterior temporal areas in the dominant hemisphere (Spitsyna et al, 2006), suggesting that *GRN*-PPA may be a dual-pathway disease although caution is clearly required in interpreting these findings, due to the small number of patients studied.

In summary, the nonfluent variants have neuroanatomical profiles that are consistent with the clinical and neuropsychological features of the syndromes. The LPA and *GRN*-PPA profiles overlap with PNFA but are distinguished chiefly by more extensive involvement of posterior elements of the language network. As with any disorder producing aphasia, the nonfluent variants provide information about the organisation of language networks that is complementary to functional imaging studies in healthy subjects, by delineating areas that are critical for (rather than simply associated with) particular functions. Both the LPA and *GRN*-PPA syndromes are clinico-anatomical entities that have a profile of brain damage complementary to the previously described disorders of SD and PNFA (described in detail in Chapter 3).

5.4 Case studies in progranulin-associated primary progressive aphasia

Two of the patients with *GRN* mutations described in Chapters 5.2 and 5.3 were studied in greater detail: Case 1 was symptomatic at first assessment and was studied in detail using a series of neuropsychological tests to further elucidate some of the underlying cognitive deficits; however, Case 2 had been followed for a number of years prior to the onset of this study as a presymptomatic member of an autosomal dominant FTLD family and during the period of this study she was assessed three further times becoming symptomatic between the first and second of these assessments thus allowing a unique opportunity to study presymptomatic and early neuroanatomical and neuropsychological deficits in *GRN*-PPA.

5.4.1: CASE 1

Clinical details

A 62-year-old right-handed male retired shopkeeper, GAA, presented with a three year history of progressive word-finding difficulty. He would break off in mid-sentence, unable to find the words to finish, and would often say the opposite of what he meant (e.g. 'yes' for 'no', 'left' for 'right', 'small' for 'big'). His speech became very sparse and he would overuse stereotyped phrases such as 'at some stage' and 'it's aggravation'. He had difficulty repeating things told to him, understanding complex instructions and remembering messages. Early on in the illness he developed problems with arithmetic and subsequently also with reading, writing and spelling. He had no other cognitive symptoms. However, his family had noted he had become more socially withdrawn in recent years and less motivated. There was no family history of dementia in his parents (his mother died at the age of 80 of cancer and his father died at 70 of cardiac disease) however two of his mother's sisters developed dementia in their 80's and his mother's father had died after some time in a psychiatric hospital.

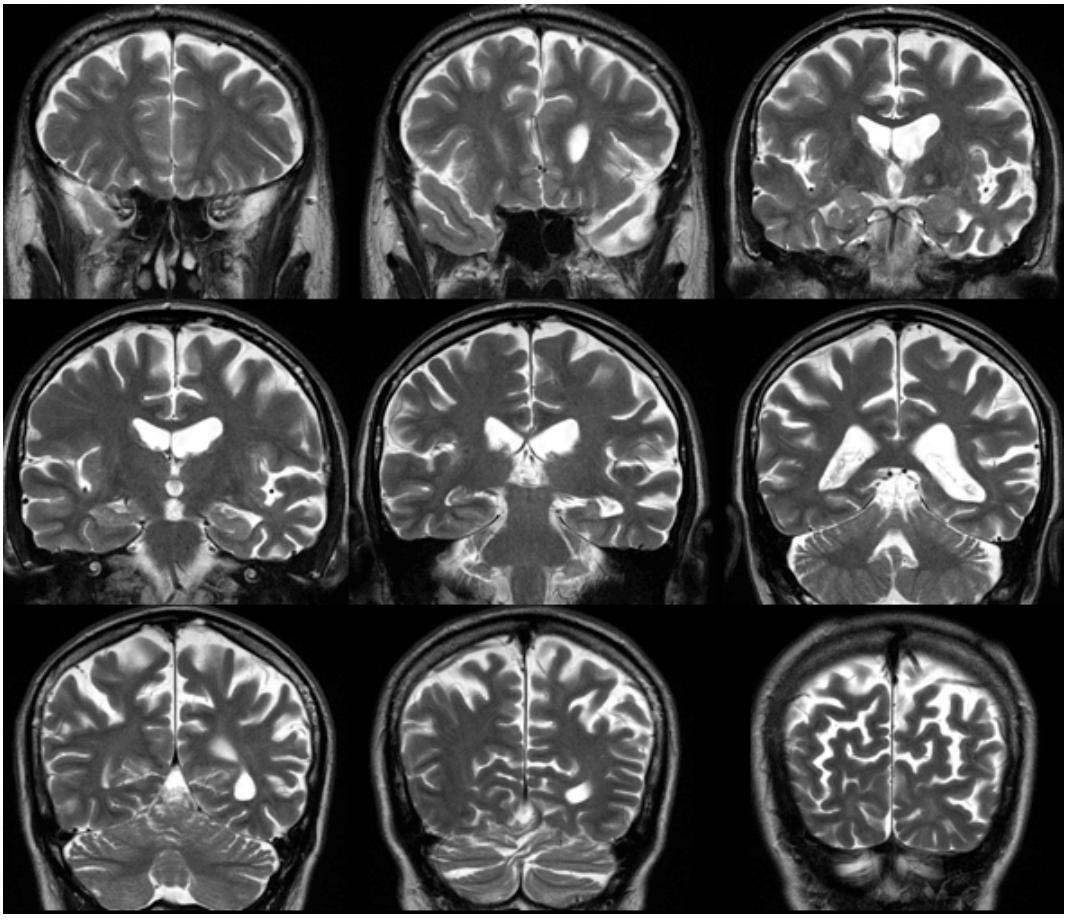
On examination he scored 19/30 on the MMSE (Folstein et al, 1975) and 13/18 on the Frontal Assessment Battery (Dubois et al, 2000). There was mild bilateral ideomotor and ideational limb apraxia. The general neurological examination was unremarkable. He had a Clinical Dementia Rating (CDR)-total of 0.5 and CDR-sum of boxes of 4.0 (Morris, 1993). On a

behavioural assessment, his total Neuropsychiatric Inventory score (Cummings et al, 1994) was 13, scoring 6 on depression/dysphoria, 2 on anxiety, 3 on apathy/indifference and 2 on irritability/lability subscales.

Brain MRI was performed three years after symptom onset (Figure 5.4.1). This showed asymmetric atrophy predominantly involving the left cerebral hemisphere and accentuated in the temporal lobe (particularly the superior and lateral temporal cortex) and parietal lobe (supramarginal and angular gyri) with additional left prefrontal lobe atrophy. Changes of cerebrovascular disease were minimal. Following this study, he required a permanent pacemaker for cardiac conduction disease, precluding serial MR imaging.

Figure 5.4.1

Coronal T2 magnetic resonance sections of GAA's brain (left hemisphere shown on the right) three years after symptom onset, showing predominantly left fronto-temporo-parietal atrophy



A blood sample was obtained as part of a study into the genetics of young-onset dementia. All 13 exons of the *GRN* gene were sequenced in at least one direction. Analysis of electropherogram traces revealed the R493X mutation, the most common *GRN* mutation reported to date (Rademakers et al, 2007).

Neuropsychological and neurolinguistic functions were investigated in detail between 36 and 42 months following symptom onset.

General neuropsychology

There was a large discrepancy between GAA's very impaired verbal IQ score and average performance IQ score (on WAIS-III, Wechsler, 1981) (See Table 5.4.1). He was tested on four separate tests from The Camden Memory Tests battery (Warrington, 1996): his performance was below the 5th percentile on a test of verbal memory whereas visual memory was intact (10th to 25th percentile on a recognition memory test for faces, 95th percentile on a topographical recognition memory test and an errorless performance on a pictorial recognition memory test). Executive functions were relatively intact on two separate tests and performance was normal on tests of visuoperceptual and visuospatial skills (Warrington et al, 1991). However he was unable to score on the Graded Difficulty Calculation Test (Jackson et al, 1986).

Table 5.4.1

General neuropsychological assessment of case GAA

Test	Score	Percentile score
General intelligence		
WAIS III verbal IQ	53	
WAIS III performance IQ	102	
Episodic memory		
Short Recognition Memory Test for Words	18/25	<5th
Short Recognition Memory Test for Faces	20/25	10-25th
Topographical Recognition Memory test	28/30	95th
Pictorial Recognition Memory test	30/30	>10th%
Executive function		
Trail Making Test A scaled score	7	10-25th
Trail Making Test B scaled score	10	50th
D-KEFS Design Fluency composite scaled score	8	10-25th
Visuoperceptual/visuospatial skills		
Visual Object and Space Perception battery (VOSP) test 3 Object decision	19/20	>75%
VOSP test 5 Dot counting	10/10	>5%
Arithmetic		
Graded Difficulty Calculation Test	0/24	<5th

Speech assessment

Propositional speech

GAA's propositional speech was gravely impaired. He volunteered little spontaneous speech. At his first clinical assessment he was asked to describe his last holiday:

> "I went to… the USA… for… *(long pause)* Boston… round there… we did round there… *(long pause)* we *you-sted* the… *(long pause)* all." (48 seconds)

When asked to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination (Goodglass et al, 1983) he volunteered:

> "This is falling out… they wanted that… they falling that… this was water… *(long pause)* that's about it I think… this was… this was along there… that's about it." (30 seconds)

Analysis of these two short samples of spontaneous speech (total time 1.3 minutes) revealed a speech rate of 33 words/minute (in nine cognitively-normal male controls with mean age 68, who spoke for an average of 2.6 minutes, the range was 102-148 words/minute). The mean log frequency of the words (based on the CELEX database, Baayen et al, 1993) used was 3.41 (control range 2.24 to 2.73), mean log frequency of nouns (also based on CELEX database) used was 2.58 (control range 1.63 to 1.97) and noun imageability (based on the MRC database) was 596 (control range 509 to 574). There were no features of speech apraxia and the speech diadochokinetic rate was normal (Apraxia Battery for Adults-2 subtest 1: Dabul, 2000). There were relatively few speech production errors although there were rare phonemic and semantic errors. Although GAA's spontaneous speech was sparse and assessment for the presence of agrammatism was therefore difficult, there were nevertheless occasional clearly agrammatic errors, e.g. "we did round there" and "they falling that". GAA was unable to perform sentence completion tasks given a sentence frame, even when the completing word was high probability (e.g. He loosened the tie around his [neck]). On a second assessment six months after the initial assessment, GAA's spontaneous speech was even more severely impoverished – attempting to describe his last holiday he said:

> "It's aggravation… *(long pause)* it's… can't do the… *(long pause)* along there… can't do… it's aggravation" (45 seconds)

Describing the Cookie Theft Picture he said:

> "That along there… along there, that's… that's…*(long pause)* see I don't these… *(long pause)* I know what it is but I can't do it, you know, it's aggravation" (35 seconds)

Detailed linguistic assessment

Naming

GAA was severely anomic scoring below the 1st percentile on the Graded Naming Test (McKenna & Warrington, 1980) (see Table 5.4.2). On a category naming test comprising high frequency nouns (Crutch et al, 2007) he had more difficulty with body parts than with animals, objects or colours. On a test comparing the naming of nouns (objects) and verbs (action pictures) matched for frequency using the CELEX database, performance was more impaired for verbs than nouns (χ^2=4.33, p=0.04). On analysis of errors made, he would commonly provide

no answer, but when attempting an answer made mainly phonemic errors (e.g. 'cheet' for sheep; 'flad' for flag, 'theeze' for tweezers) and only occasional semantic (descriptive) errors (e.g. 'red bits' for bird (robin)).

Table 5.4.2

Detailed linguistic assessment: naming

Test	Score	Percentile score/ normal range (NR)
Graded Naming Test	4/30	<5th
Category naming test	23/40	
Animals	7/10	NR 8-10
Objects	6/10	NR 10
Colours	7/10	NR 9-10
Body parts	3/10	NR 10
Matched noun and verb naming test		
Nouns	6/20	NR 18-20*
Verbs	1/20	NR 18-20*

*Normal range based on a cognitively-normal control sample of 18 patients (9 male, 9 female) with an average age of 67.9.

Speech repetition

GAA's repetition of both single words and sentences was impaired (See Table 5.4.3). Single word repetition showed a small but non-significant frequency effect (43/60 high frequency; 35/60 low frequency, χ^2=2.34, p=0.13) and a significant effect of syllable length (31/40 one syllable words; 28/40 two syllable words; 19/40 three-syllable words, χ^2=8.57, p=0.01) (see Table 4.3.3). Analysis of his 42 repetition errors revealed 11 items with no response (26%) and 31 phonological errors (11 substitutions (26%), 11 omissions (26%), 3 additions (7%), 1 transposition (2%) and 5 with multiple errors). There were also errors repeating nonwords (13/20). Sentence repetition was severely impaired (0/10): GAA was unable to repeat any of 10 short sentences or 10 clichés. In general he provided no response, however examples of errors made included:

IT WAS TOO HOT too hot

DEAF AS A POST deaf as a front

Table 5.4.3

Detailed linguistic assessment: single word repetition

Test*			
Single word repetition: 78/120	*1 syllable*	*2 syllable*	*3 syllable*
High frequency	17/20	16/20	10/20
Low frequency	14/20	12/20	9/20

*Ceiling performance for all repetition tasks in cognitively-normal controls

Single word comprehension

GAA's performance was assessed on a series of single word comprehension tests, some of which involved direct matching between a word and target, and other tests which involved a degree of associative knowledge. GAA's performance on these comprehension tasks was variable (See Table 5.4.4). Thus his performance on the verbal (spoken and written input) version of the Pyramids and Palm Trees test (Howard et al, 1992) was impaired, and furthermore significantly inferior to his performance on the visual version of the task which was within the normal range (Sign test: N=11, x=2, p=0.03). Similarly he had difficulty on the verbal version of the Camels and Cactus test (Bozeat et al, 2000) compared with his normal score on the visual version (Sign test: N=17, x=4, p=0.03). GAA also attempted the short version of the British Picture Vocabulary Scale (Dunn et al, 1982), and he scored below the 5th percentile with both written word and spoken word presentation. By contrast, on a test of semantic knowledge that probed attributes of size and weight in animals and objects respectively (Warrington et al, 2007) he scored at a normal level on both the verbal and visual versions of the test. He was also assessed on the Category Specific Names Test assessing single word comprehension (McKenna, 1998): this test comprises arrays of five pictures selected from 4 categories, graded in difficulty so that the range of items encompasses very low frequency objects: on each section of this test (both spoken and written name to picture matching), he

scored above the average level. He also attempted four graded 2-choice (spoken and written) synonym comprehension tests, involving concrete and abstract nouns and verbs (Warrington et al, 1998; Manning et al, 1995). He was clearly impaired on both the verb versions of the test (scores not meaningfully different from chance) but within the normal range for both concrete and abstract nouns. He performed well on the Graded Naming Test presented as a forced 3-choice recognition task in which he was presented simultaneously with a spoken and written definition for each item (e.g. "What is the large canvas covered frame upon which children can bounce and jump? – TARPAULIN, TAMBOURINE or TRAMPOLINE").

Table 5.4.4

Detailed linguistic assessment: single word comprehension

Test	Score	Percentile score/ normal range (NR)
Pyramids and Palm Trees test		
Verbal∗ (3 words)	43/52	NR 49-52
Visual (3 pictures)	50/52	NR 49-52
Camels and Cactus test		
Verbal∗ (5 words)	46/64	NR 56-63
Visual (5 pictures)	55/64	NR 51-62
British Picture Vocabulary Scale (short)		
Written word to picture matching	21/32	<5th
Spoken word to picture matching	24/32	<5th
Size/Weight Attribute test		
Verbal Animals	30/30	NR 26-30
Visual Animals	29/30	NR 27-30
Verbal Objects	27/30	NR 26-30
Visual Objects	29/30	NR 26-30
Category Specific Names Test		
Written presentation		
Fruit	30/30	Control mean 25.0$^{\#}$
Animals	30/30	Control mean 28.3$^{\#}$
Praxic objects	26/30	Control mean 29.2$^{\#}$
Non-praxic objects	30/30	Control mean 26.8$^{\#}$
Spoken presentation		
Fruit	25/30	Control mean 24.8$^{\#}$
Animals	30/30	Control mean 28.2$^{\#}$
Praxic objects	30/30	Control mean 29.2$^{\#}$
Non-praxic objects	29/30	Control mean 26.7$^{\#}$
Warrington synonyms test∗		
Concrete nouns	21/25	50-75th
Abstract nouns	18/25	10-25th
Concrete verbs	15/25	Control mean 22^{+}
Abstract verbs	15/25	Control mean 20^{+}
Graded Naming Test from description (forced choice of 3 words)∗	23/30	

∗presented simultaneously in both spoken and written form, $^{\#}$based on control sample of 10 subjects from McKenna & Parry, 1994, $^{+}$based on control sample of 3 subjects from Manning & Warrington, 1995

Sentence comprehension and grammar

GAA's performance was below the 5th percentile on the Test of Reception of Grammar (TROG, Bishop, 1989). On a further set of 24 sentences taken from PALPA55 (Kay et al, 1992) his performance was significantly worse on reversible than nonreversible sentences and on passive than active sentences. Furthermore, performance was worse for sentences containing directional motion verbs (where one of the distractors was the opposite motion e.g. push versus pull) compared with sentences with non-directional verbs. GAA's comprehension of verb tense was explored using an adapted version of the Lesser/Parisi and Pizzamiglio syntax test (Lesser, 1974; Parisi et al, 1970) comprising 20 pairs of pictures which differ in whether the agent is doing something/has done something (present/past comparison, 10 items) or whether the agent is doing something/is about to do something (present/future comparison, 10 items). He scored 16/20 on this task scoring equally on the present/past and present/future items (healthy controls score at or near ceiling on this test). GAA was also tested on a grammaticality judgment test which was an adapted version of the Test for Syntactic Abilities (Quigley et al, 1978): this test entails a two-alternative forced choice on two sentences (presented simultaneously both visually and aurally), one of which is grammatical and the other agrammatical. The agrammatical sentences contained a variety of errors including incorrect verb tense, addition/substitution/deletion of function words and incorrect word order. GAA scored 79% on this test making 23 errors of which 15 were errors made on incorrect verb tense (See Table 5.4.5).

Table 5.4.5

Detailed linguistic assessment: sentence comprehension and grammar

Test	Score	Percentile score/ normal range* (NR)
Test for the Reception of Grammar (TROG)	45/80	<5th
PALPA 55 (modified version)	17/24	NR 22-24*
Reversible	63%	
Non-reversible	88%	
Passive	58%	
Active	83%	
Directional	50%	
Non-directional	75%	
Verb tense comprehension test	16/20	NR 19-20*
Test of syntactic abilities (modified)	85/108	

*Normal range based on a cognitively-normal control sample of 18 patients (9 male, 9 female) with an average age of 67.9.

Reading

GAA was able to read single letters fairly competently with only 1 error from 25 letters (See Table 5.4.6). However he had great difficulty reading both real words and nonwords (Snowling et al, 1996). Investigating his real word reading further, he had similar difficulty reading regular and irregular words. He had greater difficulty with abstract words than concrete words and with increasing word length. A battery of 275 3-letter words was also administered to examine reading errors: he read 77% of the words correctly, with 62 errors in total. Included in this test were 55 3-letter function words: there were errors on 29% of these words (compared with 21% errors on the other 220 content words). There was a mixture of error types across the reading subtests, comprising mainly phonological (e.g. 'opperosite' for opposite) and visual (e.g. 'December' for decent) errors but also occasional regularisation (e.g. 'gem' with hard 'g' for gem), and semantic errors (e.g. 'salt' for sour).

Writing and spelling

GAA's spelling was severely impaired. He was unable to score on the written Graded Difficulty Spelling Test (Baxter et al, 1994) (see Table 5.4.6). His attempts for the first four items were 'ONE' for TWO, 'BULL' for WORLD, 'SEA' for SAID and 'NICE' for SHOE. On a further set of 3–letter words he scored equally poorly on both regular and irregular words and oral and written spelling were comparably affected. He made seven errors on oral spelling, comprising five no responses and the errors 'SIK' for SEA and 'SAT' for CAP; and six errors on written spelling, comprising single letters: 'S' for SON and SAW, 'M' for CUP, 'W' for LOG and 'M' for BAR. On attempting to write single letters to dictation he was able to produce only five of 25 letters.

GAA was asked to construct grammatical sentences containing each of 10 written target words. He made no attempt for three words ('new', 'radio', 'tree'), and for the remaining seven words produced the following:

EARLY	Early a clock eight
CAUGHT	Caught a sam
PUSHED	Pushed on door
SMALL	Small emp
WALKED	Walked a patio
THROW	Throw on door
BLUE	Blue door

Table 5.4.6

Detailed linguistic assessment: literacy skills

Test	Score*
Reading	
Single letter reading	24/25
National Adult Reading Test	0/50 (<1st %)
Graded difficulty nonword reading test	2/20 (<10th %)
Coltheart irregular vs regular word reading test	31/78
Irregular words	15/39
Regular words	16/39
Concrete/abstract reading test	47/72
Abstract words	18/36
Concrete words	29/36
High frequency words	23/36
Low frequency words	24/36
1 syllable length	21/24
2 syllable length	17/24
3 syllable length	9/24
Writing/Spelling	
Sentence construction	0/10
Graded difficulty spelling test	0/30 (<1st %)
3-letter word spelling test	7/20
Regular words	5/10
Irregular words	2/10
Oral spelling	3/10
Written spelling	4/10
Single letter writing	5/25

*All cognitively-normal adults score at a ceiling level on tests apart from the NART, Graded difficulty nonword reading test and Graded difficulty spelling test.

Short term memory

GAA's digit span, assessed as part of the WAIS-III, was severely impaired (See Table 5.4.7). His auditory-verbal digit span, auditory-verbal letter span, auditory-verbal word (3-letter, one-syllable) span, visual-verbal digit span and spatial span were subsequently compared. In each

condition, eight trials were presented with 1, 2 or 3 items. GAA was unable consistently to repeat more than 1 item for spoken digits, letters or words. Performance was better for visually presented digits, for which he was occasionally able to repeat 3 items. Furthermore, in stark contrast to his performance on the auditory tasks, his spatial span (assessed with the Corsi block-tapping test, Corsi, 1972; Kessels et al, 2000) was within the normal range – he was able to point without error to 3 blocks, scored 4/8 completely correct trials (24/32 positions) with four blocks and 1/8 completely correct trial (22/40 positions) with five blocks.

Table 5.4.7

Short term memory assessment

Task	1 item	2 items	3 items
Auditory-verbal digit span	6/8	1/8 (5/16)	Unable
Auditory-verbal letter span	7/8	*Phonologically similar* 1/8 (6/16)	Unable
		Phonologically dissimilar 0/8 (3/16)	
Auditory-verbal word span	5/8	0/8 (3/16)	Unable
Visual-verbal digit span	7/8	6/8 (14/16)	2/8 (15/24)
Spatial span	8/8	8/8 (16/16)	8/8 (24/24)

8 stimuli for each task at each level. Scores are shown as total completely correct out of 8 and in brackets the total number of items in the correct position (out of 16 for 2 items and 24 for 3 items).

DISCUSSION

This case report describes in detail the pattern of neuropsychological and linguistic deficits in a patient with *GRN*-associated PPA. The salient clinical features were sparse, slow and impoverished spontaneous speech with word-finding pauses. The profile of neuropsychological deficits comprised severe anomia, poor verbal short-term memory and impaired sentence comprehension, associated with dyslexia, dysgraphia and dyscalculia. By contrast certain (non-

associative) aspects of single word comprehension, nonverbal memory and visual perceptual skills were well preserved. The constellation of neuropsychological findings in GAA constitutes a distinctive pattern of cognitive impairment and preservation: the clear verbal modality specificity of GAA's language deficits indicates preferential involvement of the dominant hemisphere, while the association of dyslexia, dysgraphia and dyscalculia constitutes a classical left parietal syndrome; the lobar localisation for other features, such as anomia and impaired phonological memory, is less clear. This neuropsychological syndrome overlaps in a number of respects with previous descriptions of the LPA syndrome (Gorno-Tempini et al, 2008) while the presence of grammatical errors in spontaneous speech and markedly impaired speech repetition suggests an additional overlap with the PNFA syndrome. However, the cognitive profile exhibited by GAA should not be regarded simply as a variant or a composite of other PPA syndromes: key features of this profile in relation to LPA and PNFA are summarised in Table 5.4.8.

Table 5.4.8

Comparison of neuropsychological features in GAA compared to LPA and PNFA

Neuropsychological feature	GAA	LPA	PNFA
Spontaneous speech	Slow, sparse spontaneous speech with word-finding pauses	Slow spontaneous speech with word-finding pauses	Speech characterized by hesitancy and effortfulness due to apraxia of speech and/or agrammatism
Naming	Severely anomic	Anomic	Mildly anomic
Single word repetition	Moderately impaired	Relatively intact (compared to sentence repetition)	Mild to moderately impaired
Sentence repetition	Severely impaired	Impaired	Impaired
Single word comprehension	Impaired for associative verbal semantic tasks	Relatively intact	Intact early in the course
Sentence comprehension and grammar	Severely impaired Possible true grammatical deficit (expressive and receptive)	Impaired	Impaired
Reading	Deep/phonological dyslexia	Phonological dyslexia	Little studied but phonological dyslexia described
Verbal short-term memory	Severely impaired	Severely impaired	Usually intact early
Episodic memory	Impaired verbal, intact nonverbal	Few studies but evidence of mild verbal impairment	Intact

Anatomically, although detailed correlation was not possible, cerebral atrophy in this case involved the left posterior temporal/anterior parietal region and also left inferior frontal areas (Figure 5.4.1). According to the current dual stream model of cortical language processing, a ventral pathway involved in processing word meaning links the superior temporal gyrus to

middle and inferior temporal gyri, temporal pole and inferior frontal cortex; while a dorsal pathway involved in articulation-to-sound mapping links the superior temporal gyrus with inferior parietal and inferior frontal cortices (Hickok et al, 2004; Warren et al, 2005; Saur et al, 2008). Following this formulation, and taking the neuropsychological and neuroimaging evidence into account, it is proposed that *GRN*-associated PPA in this case is likely to reflect involvement of both the dorsal and ventral language pathways, with a key site of overlap in the region of the temporo-parietal junction. The evidence is now considered for this claim in more detail.

GAA had progressive anomia. While this is likely to be attributable at least in part to impaired word retrieval, a verbal semantic deficit may also have contributed. GAA's variable performance on single word comprehension tests is relevant both to neuropsychological theories of semantic knowledge as well as to how such a syndrome would fit into current PPA classifications. He had no difficulty with the Size/Weight Attribute Test of conceptual knowledge and more impressively he scored at a high level on both the spoken and written word versions of the Category Specific Names Test probing knowledge of low frequency items. Furthermore, on a synonyms test of concrete noun comprehension his performance was at an average level. By contrast, on word-picture matching tests such as the British Picture Vocabulary Scale where the mapping between word and target picture is less direct, his performance was impaired. He was also impaired on verbal (spoken and written word to word) matching tasks such as the verbal versions of the Pyramids and Palm Trees and Camels and Cactus tests whilst exhibiting normal performance on the visual versions. How can one explain the profile of dissociated verbal semantic impairments observed in GAA?

Considering first the word-picture matching tests, one could suggest that GAA's weaker performance is observed on those tasks involving some degree of associative rather than direct semantic matching. Such tasks are likely to involve executive control processes, as suggested by Jefferies et al, 2006. However, a primary deficit in executive control would not easily explain the difference between GAA's performance on verbally and visually mediated versions of these associative tasks. This visual advantage is in contrast to the pattern of performance

described in stroke patients (Jefferies et al, 2006; Corbett et al, 2009), and belies the equal semantic control demands of the visual and verbal versions of this task. Another possibility is that GAA has mildly impaired lexical semantics, such that response selection among closely related alternatives is required to expose degraded semantic representations; or alternatively, an intact semantic store but a deficit in linking phonological representations of words with their meanings, which is exposed when the semantic targets are more closely related. Picture-picture matching might provide additional information or cues unavailable from the written or spoken word, with correspondingly better performance on visual than verbal matching tasks. An explanation of this kind would be in line with evidence from studies of focal lesions such as stroke affecting associative cortical areas in the region of the temporo-parietal junction (Hillis, 2007). Moreover, degraded access to semantic stores resulting from posterior temporal-inferior parietal lobe atrophy would be consistent with functional imaging evidence in healthy subjects suggesting that the extraction of meaning from both spoken and written language may require connectivity between posterior and anterior temporal lobe areas in the ventral language stream (Spitsyna et al, 2006).

A test such as Pyramids and Palm Trees seems to call for manipulation of verbal concepts and contexts (e.g. in order to decide whether "cat" or "dog" is the correct answer when presented with "mouse", one must not only comprehend individual concepts but also activate the salient relationships between target and response i.e. "hunter/hunted" rather than "both animals" or "don't bark" etc.). The further possibility is therefore raised that the dissociation between verbal and non-verbal comprehension performance observed in GAA may arise from a selective deficit of verbal reasoning. 'Verbal reasoning' is itself an under-specified term: it is used here to embrace several potentially relevant processes, such as inference or abstraction of a semantic relationship that is not directly implied by the stimuli. That such processes can be specific to the verbal modality is supported by the existence of a selective deficit of verbal message formulation in patients with so-called "dynamic aphasia" (Costello et al, 1989; Warren et al, 2003). The present study does not disambiguate any deficit in verbal reasoning from a mild deficit of lexical semantics (indeed, that distinction is difficult even in principle). However, processes such as verbal inference are likely to involve fronto-parietal circuitry (Reverberi et al,

2007), raising the possibility that the associative verbal semantic deficit identified in GAA might implicate either the dorsal or the ventral language pathway (or indeed, a conjoint deficit attributable to temporo-parietal junction damage).

GAA showed evidence of an impaired phonological store (poor verbal short term memory). His auditory verbal span was not entirely intact even for single items (digits, letters or words), while visual verbal span was only marginally better. This contrasted with his normal visuospatial span. In addition, GAA's performance was impaired on tests not only of receptive grammar (e.g. TROG, PALPA55) but also grammaticality judgement tests (e.g. Test of syntactic abilities). Previous evidence suggests that although they may cause deficits in sentence comprehension tasks, auditory verbal span deficits are neither necessary nor sufficient to produce such deficits in receptive grammar and grammaticality judgements (e.g. Shallice et al, 1977; Caplan et al, 1999). It is proposed that GAA has a double deficit affecting both his auditory verbal short term memory and the systems mediating receptive grammar. This would also be consistent with the distributed pattern of left cerebral atrophy with left temporo-parietal emphasis in this case: the phonological store is likely to be mediated by anterior inferior parietal and posterior superior temporal areas whilst sentence and grammatical processing are associated with inferior frontal and posterior superior temporal areas (Vigneau et al, 2006; Buchsbaum et al, 2008). Sentence comprehension has been studied in LPA with suggestions that deficits are secondary purely to phonological store deficits (Gorno-Tempini et al, 2008). However, there have been no previous studies attempting to dissociate a true receptive grammatical deficit from a phonological store deficit in LPA (e.g. on a grammaticality judgment test). Similarly, it has been difficult to characterize any expressive agrammatism in LPA, as speech tends to be sparse with prolonged pauses. In this study there was some evidence for agrammatism in GAA's spontaneous speech and further evidence in his production of very simple or agrammatic sentences in writing. This may represent a further distinction from the LPA syndrome, (suggesting an overlap with the classical PNFA syndrome) but again, will require further study, particularly with detailed quantitative analysis of spontaneous speech and writing in this group.

With further regard to his deficit of receptive grammar processing, GAA had particular difficulty with comprehension of verb tense which, in conjunction with poor performance on verb naming and verb comprehension tasks, suggests a relatively selective deficit of verb (versus noun) processing. Anatomically, verb processing is thought to rely on left dorsal language pathway areas including left prefrontal cortex (Damasio et al, 1993) and posterolateral temporal cortex (Grossman et al, 2002), consistent with the pattern of atrophy seen here. Of note, a selective deficit in verb processing has been previously described in a familial ubiquitin-positive inclusion dementia (Bak et al, 2006): although the genetic diagnosis in this previous case was not defined, considered together these observations raise the possibility that defective verb processing may be a signature of *GRN* mutations in PPA.

GAA exhibited additional deficits of literacy skills that provide further evidence of deficient phonological processing. His reading deficit shows the typical pattern of deep/phonological dyslexia affecting regular and irregular real words as well as nonwords, the errors produced being a mixture of phonological, visual and more rarely regularisation and semantic errors, with better performance reading concrete compared to abstract words (Coltheart, 1980; Crisp et al, 2006). Similarly his pattern of spelling deficits indicates phonological dysgraphia in both oral and written modes. The presence of phonemic errors would be consistent with a deficit of phonological transcoding, which may result from damage to the left temporo-parietal junction. Patients with LPA have previously been described as having phonological dyslexia (Brambati et al, 2009a) and a more general deficit of phonological processing (Gorno-Tempini et al, 2008).

It is worth considering how this neurolinguistic and anatomical formulation may relate to other clinical features in this case and in previous descriptions of *GRN*-associated disease. GAA did not exhibit neurological signs of parkinsonism (described in around a third of *GRN* mutation cases) or motor neurone disease (a rare feature) (Baker et al, 2006; Cruts et al, 2006). However, GAA did display evidence of apathy and depression as well as increased anxiety and irritability: such behavioural changes have been previously reported with *GRN* mutations (Snowden et al, 2006) and indeed, the most common clinical phenotype of *GRN* mutations is progressive personality change (behavioural variant frontotemporal dementia) as described in

Chapter 3. Similar behavioural symptoms have been described in association with both PNFA and LPA (Rosen et al, 2006). In anatomical terms, such complex behaviours are likely to depend on distributed circuitry and might therefore be vulnerable to disease processes that strike long intra-hemispheric pathways linking frontal and anterior temporal cortices with more posterior areas, as it is proposed may underpin the *GRN*-associated aphasic syndrome here.

This case has highlighted certain neuropsychological differences with respect to previous descriptions of either the LPA or PNFA syndromes (Gorno-Tempini et al, 2004a: Gorno-Tempini et al, 2008; Brambati et al, 2009a: see Table 4.4.8), in particular, the early occurrence of single word comprehension deficits and, in comparison to LPA, expressive agrammatism. The patient had asymmetric left temporal and parietal atrophy and involvement of the key left temporo-parietal junction zone would be predicted to correlate with involvement of functionally connected regions in the left inferior frontal and anterior temporal lobes via the dorsal and ventral speech processing pathways demonstrated in functional imaging studies in healthy subjects (Scott et al, 2003) and implicated in clinical aphasia syndromes of vascular disease (Hillis, 2007; Jefferies et al, 2006).

5.4.2: CASE 2

This section describes the clinical, neuropsychological and radiological profile of a member of the DRC255 family (found to have a mutation in *GRN*) who had been followed over a thirteen-year period, from an early presymptomatic stage through the development of a progressive aphasia.

Clinical details

Case PAF is a right-handed woman followed from 55-years-old as part of a prospective longitudinal clinical and MRI study of asymptomatic individuals at-risk of developing familial autosomal dominant FTLD. She underwent a series of assessments comprising eight visits in total, each involving detailed clinical and neuropsychological evaluation and volumetric brain MRI.

Clinical assessment

Each assessment included a structured clinical interview and neurological examination including assessment of limb and orofacial apraxia. The Mini-Mental State Examination (MMSE) (Folstein et al, 1975) and Frontal Assessment Battery (FAB) (Dubois et al, 2000) were also performed.

Neuropsychological assessment

General intellectual function was tested with the WAIS (Weschler, 1981) and the VESPAR (Langdon et al, 1995). Episodic memory was tested using the Recognition Memory Test for Words and Faces (Warrington, 1984) and a test of paired associate learning (Warrington, 1996). Language function was tested using the Graded Naming Test (McKenna et al, 1980), Warrington Concrete Synonyms Test (Warrington et al, 1998) and a test of polysyllabic word repetition. Other cognitive domains assessed included calculation (Graded Difficulty Arithmetic Test: Jackson et al, 1986), visuospatial and visuoperceptual skills (subtest 2 of the Visual Object and Spatial Perception (VOSP) battery: Warrington et al, 1991) and executive

function (Modified Card Sorting test: Nelson et al, 1976). In the last four assessments tests of basic and complex facial emotion recognition were also performed (Ekman test of facial emotion recognition: Ekman et al, 1976; Gray et al, 1997; and the 'Reading the Mind in the Eyes' Test Revised Version: Baron-Cohen et al, 2001). The last test was originally devised as an 'advanced' test of mentalising ability (the ability to interpret others' mental states, or 'Theory of Mind': Baron-Cohen et al, 1997). Findings on longitudinal neuropsychological assessment are summarised in Table 5.4.9. Six months after the last annual assessment a more fine-grained assessment of language functions was performed using a range of neurolinguistic instruments (summarised in Table 5.9.10). These instruments were designed to analyse in detail the basis for any aphasic deficit.

Brain imaging

Eight T1-weighted MRI brain volumes were acquired. The first four scans and the last four scans were acquired on two different scanners, however both were 1.5T GE Signa (General Electric, Milwaukee, WI). Of note, the 5th scan was acquired prior to a scanner upgrade. All scans were processed using the MIDAS software tool (Freeborough et al, 1997a). A semi-automated technique of brain segmentation was performed for each scan followed by an affine (12 degrees of freedom) registration in order to align the repeat scan onto the baseline image where both images were taken on the same scanner (Woods et al, 1998). Whole brain atrophy rates were calculated over the inter-scan intervals using the brain boundary shift integral (Freeborough et al, 1997b) and regional atrophy was assessed using a fluid registration technique producing a voxel compression map (Freeborough et al, 1998, Fox et al, 2001) as described in chapter 2. Hemispheric volumes were also calculated as described in chapter 2. A similar procedure was performed in order to separate the lateral ventricles into right and left sides.

RESULTS

Clinical and neuropsychological findings

For the initial four visits PAF remained well with no cognitive symptoms and scored normally on neuropsychological assessment. She was lost to follow up for the next seven years but

returned for assessment 10 years after her first assessment. At this appointment (visit 5) she did not complain of any symptoms and again scored normally on detailed testing apart from a slightly reduced verbal fluency (9 'S' words in one minute) on the FAB. However a year later, at visit 6, although she still had no cognitive complaints, neuropsychometry revealed evidence of decline in naming and calculation (although the absolute scores still remained within normal limits) (Table 5.4.9).

At the next visit one year later (Visit 7, 12 years since the initial visit, when PAF was aged 67) she complained of cognitive symptoms for the first time with the onset over the previous six months of word-finding difficulty. MMSE score at this time was 28/30. Verbal fluency was reduced on the FAB (6 'S' words in one minute) and there were difficulties with sentence repetition. Graded Naming Test score was now below the 5th percentile (10/30) and further decline was evident on testing of calculation. Performance had now also deteriorated on a test of verbal comprehension but remained normal (with no deterioration in performance) on tests of executive function and visuoperceptual skills. Imitation of meaningless hand positions was a little clumsy but the neurological examination at this time was otherwise normal.

At visit 8, 18 months after symptom onset, word-finding had continued to deteriorate and PAF had developed speech production impairment with phonemic paraphasias and agrammatism. Her family reported that she had become more apathetic over the previous year and spent most of the time in her house. MMSE score was now 22/30 and verbal fluency was again reduced. There was also now mild bilateral ideomotor and ideational limb apraxia although the rest of the neurological examination remained normal. Naming had further deteriorated with the patient now scoring below the 1st percentile (3/30). Verbal memory difficulties had become more apparent with deterioration in performance on both the paired associate learning task and the Recognition Memory Test for Words.

PAF's ability to recognize both simple and complex facial emotions deteriorated from the baseline score at visit 5, 18 months prior to symptom onset (Table 5.4.9). On the 'Reading the Mind in the Eyes' test performance fell from a score of 26/36 which was within an age and sex-

matched normal range (24-34/36) to a score of 22/36 the following year, still six months prior to symptom onset. Eighteen months after symptom onset performance fell further to 18/36. On a test of basic facial emotion recognition based on the Ekman emotional faces stimulus set (Gray et al, 1997) the patient scored below the age and sex-matched control range (>20/24) even 18 months before symptom onset (19/24) and performance continued to deteriorate over the next three visits. By 18 months after symptom onset she scored only 11/24. Performance was at chance (3/16) for negative emotions (fear, disgust, anger, sadness) but normal (8/8) for positive emotions (happiness, surprise).

Table 5.4.9

Summary of neuropsychological assessments

Assessments	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Years from baseline	**0**	**1**	**2**	**3**	**10**	**11**	**12**	**13**
Years from symptom onset	**-11.5**	**-10.5**	**-9.5**	**-8.5**	**-1.5**	**-0.5**	**+0.5**	**+1.5**
MMSE	30	29	NT	29	30	30	28	22
FAB	NT	NT	NT	NT	15	15	17	15
Verbal IQ	98	109	103	105	105	112	94	85
Performance IQ	95	88	107	109	104	108	106	108
Verbal memory (/50)[a]	42	44	45	43	41	42	43	38*
Visual memory (/50)[b]	40	42	46	42	44	46	41	44
Paired associate learning (/8)	NT	NT	NT	NT	8	8	8	5*
Naming (/30)[c]	25	23	28	26	26	22	10**	3***
Word comprehension (/25)[d]	24	22	21	24	23	24	21	21
Word repetition (/15)	NT	NT	NT	NT	15	15	15	15
Calculation[e]	22/24	19/24	18/24	19/24	8/12	7/12	5/12	6/12
Visuospatial/perceptual skills[f]	26/30	26/30	28/30	27/30	13/15	12/15	12/15	12/15
Executive function[g]	pass	pass	pass	pass	pass	pass	pass	pass
Complex facial emotion recognition (/36)[h]	NT	NT	NT	NT	26	22	22	18
Simple facial emotion recognition (/24)[i]	NT	NT	NT	NT	19	18	17	11

a and b Warrington Recognition Memory Test for Words (a) and Faces (b); c Graded Naming Test; d Warrington Concrete Synonyms Test; e Graded Difficulty Arithmetic Test: total test score out of 24, addition subsection out of 12; f Silhouettes subtest 2 of Visual Object and Spatial Perception (VOSP) battery: total test score out of 30, objects only out of 15; g Modified card sorting test; h The 'Reading the Mind in the Eyes' Test Revised Version: control range 24-34 based on a sample of 18 cognitively-normal females with an average age of 67.5; i Ekman test of facial emotion recognition: control range 20-24 based on a sample of 18 cognitively-normal females with an average age of 67.5. ***<1st percentile; ** =1st to <5th percentile; * =5th to <25th percentile; NT = not tested

Detailed language assessment

In order to delineate her language difficulties more precisely, PAF underwent more detailed neurolinguistic assessment six months after visit 8 and two years after the onset of symptoms (Table 5.4.10). Simple auditory perception as assessed using a phoneme discrimination task was intact (Kay et al, 1992). Although still scoring within the normal range there was evidence of deterioration on a test of single word comprehension (Warrington et al, 1998) from the 50th percentile six months previously to the 10th percentile. The patient could now only name two items on the Graded Naming Test, scoring below the 1st percentile (McKenna et al, 1980). On a simpler novel test of noun and verb naming she managed to name 14/20 nouns and 13/20 verbs. On all tests of naming she produced multiple phonemic errors. Single word repetition (11 errors/150 words) and sentence repetition (4 errors/20 sentences) were impaired. When asked to construct a written sentence based around a single word there were grammatical errors in 4 out of 10 written sentences produced. She also had difficulty judging whether sentences were grammatical or not (10 errors/30 sentences). Reading was also affected (61/100 words on the Schonell reading test (IQ equivalent 79) Nelson et al, 1975). There was evidence of a phonological dyslexia with difficulty reading non-words (12/20 on the Graded Nonword Reading Test; Snowling et al, 1996) but no regularisation errors. Spelling was relatively intact (25-50th percentile on the Graded Difficulty Spelling Test; Baxter et al, 1994).

At this assessment, the patient was also noted to have a decreased forwards digit span of 4, consistent with dominant parietal lobe involvement, and a backwards digit span of 3. Praxis assessment using subtest 3 from the Apraxia Battery for Adults (ABA2 – Dabul, 2000) revealed moderate limb apraxia (36/50) and mild orofacial apraxia (42/50).

Table 5.4.10

Detailed neurolinguistic analysis (2 years after symptom onset)

	Score	Normal range#/percentile score
Phoneme discrimination (modified version of PALPA 3)	34/36	Normal range 33-36
Synonyms test ***Concrete words*** ***Abstract words*** ***TOTAL score***	 *17/25* *16/25* 33/50	 10th percentile 10th percentile 10th percentile
Sentence comprehension (modified version of PALPA 55)	15/24	Normal range 21-24
Grammaticality judgment test	20/30	Normal range 25-30
Graded naming test	2/30	<1st percentile
Noun and verb naming	14/20 (nouns) 13/20 (verbs)	Normal range 18-20 Normal range 19-20
Polysyllabic word repetition	139/150	Normal score 150 (all controls score at ceiling)
Sentence repetition	16/20	Normal score 20 (all controls score at ceiling)
Sentence completion	16/20	Normal range 19-20

Schonell reading test	61/100	5-10th percentile
Graded nonword reading test	12/20	Normal range 15-20
Graded difficulty spelling test	17/30	25-50th percentile
Written sentence construction	6/10	Normal range 8-10

Normal ranges based on a control sample of 18 cognitively-normal people with an average age of 67.4 consisting of 10 males and 8 females.

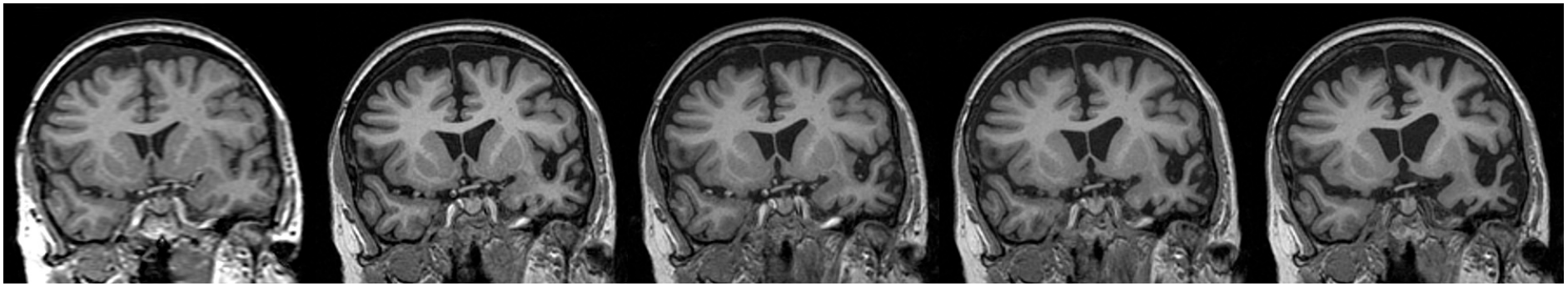
Brain imaging findings (Figures 5.4.2, 5.4.3 and 5.4.4)

There were no significant changes beyond normal ageing seen over the first four scans. However, there was a significant decrease in brain volume (Figs 5.4.2 and 5.4.4) between the 4th and 5th visit (i.e. between 9 years pre-symptoms and 18 months pre-symptoms). The 5th scan (Fig 5.4.2b) showed asymmetrical frontal, temporal and parietal lobe atrophy predominantly affecting the left cerebral hemisphere. Progressive atrophy in a similar distribution was present on the 6th scan (6 months prior to onset of symptoms: Fig 5.4.2c). Further analysis of the change between the 6th and 7th scans (6 months after the onset of symptoms) with image registration based on a fluid model resulting in voxel compression maps (as described in Chapter 2; Fox et al, 2001) (Fig 5.4.3) provided further information about the detailed distribution of volume change within the hemisphere. There was progressive regional atrophy involving the left frontal, temporal and parietal lobes (Figure 5.4.3a). In the frontal lobes there was atrophy of the medial superior frontal and frontopolar regions, and involvement of the anterior cingulate gyrus. There was marked atrophy of the left temporal pole. The left middle and inferior temporal and fusiform gyri were significantly affected, with some atrophy of left amygdala, hippocampus and superior temporal gyrus. In the parietal lobes there was relatively selective atrophy of the left angular gyrus posteriorly. There was also evidence of left caudate, pallidal and thalamic atrophy. Registration of the 7th and 8th scans (6 and 18 months respectively after onset of symptoms) showed a similar pattern but now also with involvement of the right hemisphere (Figure 5.4.3b). The most severe change across scans involved prefrontal and inferior parietal areas as well as orbitofrontal and inferior temporal areas in the left hemisphere.

Figure 5.4.2

Series of five registered T1-weighted MRI images from 8.5 years pre-symptom onset to 1.5 years after symptoms in case PAF: a) Symptom onset -8.5 years; b) Symptom onset -1.5 years; c) Symptom onset -6 months; d) Symptom onset + 6 months; e) Symptom onset + 1.5 years

2a **2b** **2c** **2d** **2e**



Symptom onset -8.5 years | Symptom onset -1.5 years | Symptom onset -6 months | Symptom onset +6 months | Symptom onset +1.5 years

Figure 5.4.3

Sagittal and coronal MRI images in case PAF with voxel-compression-mapping overlay over time period: a, Symptom onset -6 months to +6 months ; b, Symptom onset +6 months to +1.5 years

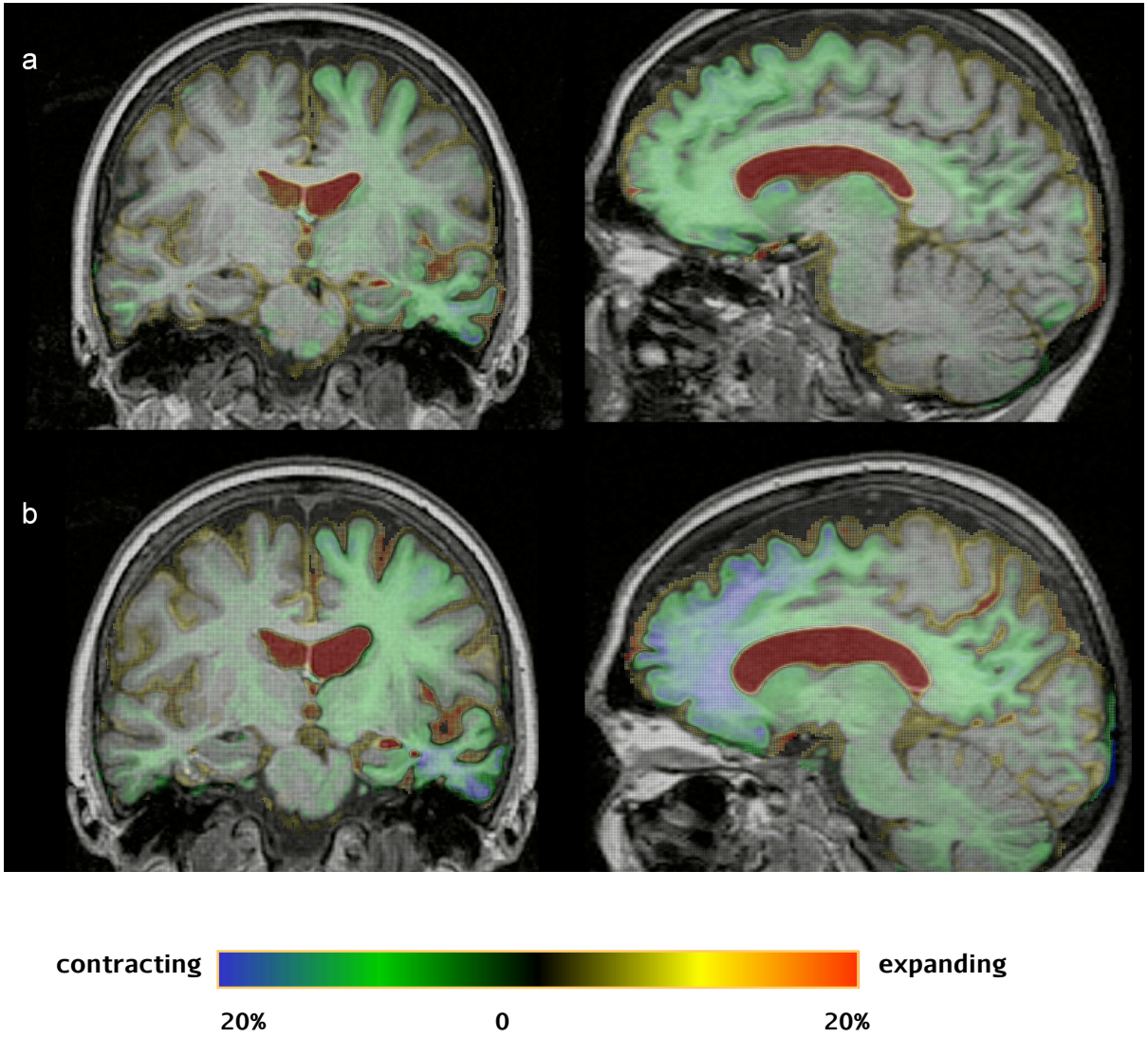
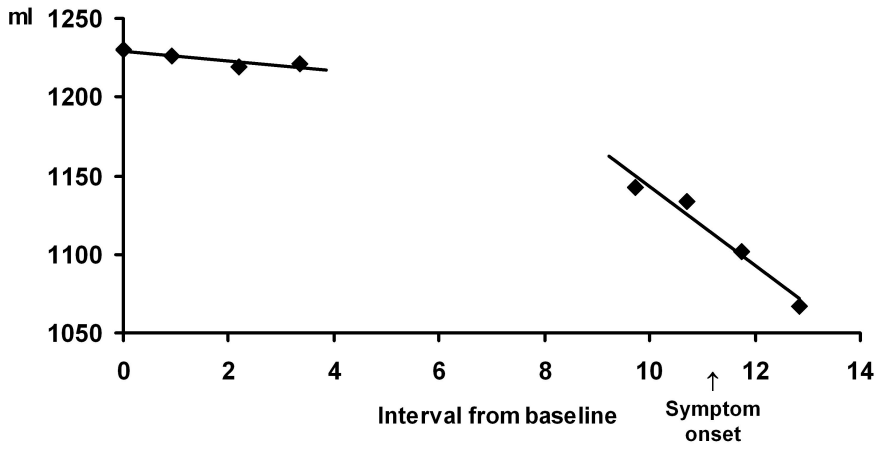


Figure 5.4.4 shows the change in whole brain (a) and individual hemisphere (b) in graphical form. These allow quantification of the regional changes observed on the longitudinal images (Figs 5.4.2 and 5.4.3), with involvement of the left hemisphere seen to precede that of the right by a number of years. Between the 7th and 8th scans, in addition to a general decrease in left hemisphere volume, there is also evidence of right hemisphere involvement (see also Figure 5.4.3b).

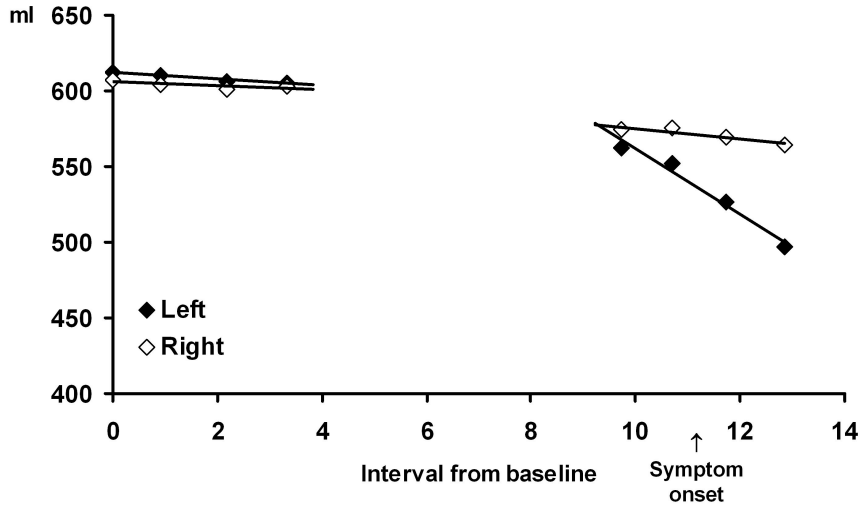
Figure 5.4.4

Whole brain (a) and hemisphere (b) volumes from baseline to 13 years after baseline.

a



b



DISCUSSION

This study describes the presymptomatic clinical, cognitive and imaging changes in *GRN*-associated PPA with a longitudinal analysis of a member of family with the C31fs mutation in the *GRN* gene over a thirteen year period from an initial asymptomatic phase through to the establishment of clinical disease. Evidence of neuropsychological impairment and brain atrophy predated the onset of clinical symptoms by at least 6 months and 18 months respectively. In keeping with the cognitive and behavioural phenotype described in the previous *GRN* case in Section 5.4.1 a progressive aphasia and parietal lobe deficits were early and salient features in this case. Brain imaging in this case further emphasizes that posterior atrophy including temporo-parietal junction areas are an early feature of disease and that atrophy is strikingly asymmetrical early in disease (see figures 5.4.2 and 5.4.3).

Correlation of longitudinal clinical, neuropsychological and brain imaging evidence in the present case allows us to analyse in greater detail the anatomical and pathophysiological effects of *GRN*-associated disease. Early, strikingly asymmetric involvement of the left cerebral hemisphere is a feature both of the cognitive phenotype and the neuroanatomical phenotype as assessed on serial MRI (Borroni et al, 2008a). The most severe deficits implicate dominant frontal lobe mechanisms mediating word retrieval and propositional speech, parietal lobe mechanisms mediating praxis, speech repetition and calculation, and orbitofrontal:anterior temporal lobe mechanisms involved in emotion processing (it is noteworthy that the tests used to assess emotion recognition in this study both required verbal mediation). The neuroanatomical distribution of heaviest disease burden followed the pattern predicted from the neuropsychological profile, with earliest and maximal change in prefrontal, inferior parietal, orbitofrontal and inferior temporal cortical areas in the left hemisphere. Furthermore, these areas form part of non-contiguous but anatomically and functionally linked intra-hemispheric networks, or pathways: a dorsal pathway linking prefrontal and parieto-temporal areas, implicated in the programming of speech and voluntary action (Warren et al, 2005) and a ventral pathway (or pathways) linking anterior and inferior temporal areas with inferior frontal areas, implicated in different aspects of semantic knowledge, emotion and social behaviour (Scott et al, 2003; Adolphs, 2003). Anatomical linkages between the components of

these functional pathways have been demonstrated in human tractography and functional imaging studies (Catani et al, 2005) and are supported by an extensive literature in non-human primates, suggesting that such pathways process distinct aspects of visual and other sensory information and behaviour (Ungerleider et al, 1982; Rauschecker et al, 2000).

This case (as well as Case 1 above) also suggests that the pathophysiological profile of *GRN*-associated disease arises from progressive breakdown of functionally linked intra-hemispheric networks. This would account both for the early involvement of anatomically remote (but linked) anterior and posterior areas within a hemisphere, and the striking asymmetry of disease burden which can remain largely restricted to a single hemisphere for many years. The functional correlates of damage involving the pathways of the right hemisphere are less clear than those of left hemisphere disease, but are likely to include deficits of goal-directed behaviour (Warren et al, 2005), as observed in other patients with *GRN*-associated FTLD. At a neuronal level it remains to be explained why *GRN* mutations cause such a phenotype and little is known about the normal role of *GRN*. However, given that *GRN* acts on wound healing and inflammation in the periphery (Ahmed et al, 2007), and has neurotrophic properties *in vitro* (Daniel et al, 2000), it is likely to act as a CNS growth factor. As suggested in Chapter 4, one could speculate that asymmetry in the clinical manifestations of *GRN* null mutation might be caused by asymmetrical expression of *GRN* from the wild-type allele or asymmetrical expression of factors that modify the downstream pathogenesis. The breakdown of functionally linked networks might be accounted for by interdependency of these neural systems on *GRN* for survival. Future work is needed including larger longitudinal case series, more detailed analysis of non-verbal and behavioural deficits in these patients and the use of complementary metabolic and functional imaging modalities to assess *GRN*-associated cerebral dysfunction directly.

5.5 Alzheimer pathology and primary progressive aphasia

As discussed in Chapters 5.1 and 5.2, whilst most cases of PPA have a pathological substrate within the frontotemporal lobar degeneration spectrum, i.e. associated with tau- or TDP-43-positive cellular inclusions (Knibb et al, 2006; Snowden et al, 2007a), it has long been recognised that PPA syndromes may be associated with Alzheimer's disease (AD) pathology (Pogacar et al, 1984; Green et al, 1990; Kempler et al, 1990; Karbe et al, 1993; Greene et al, 1996; Li et al, 2000; Clark et al, 2003) and in recent years more detailed series have been reported (Galton et al, 2000; Croot et al, 2000; Davies et al, 2005; Knibb et al, 2006; Alladi et al, 2007; Josephs et al, 2008b; Mesulam et al, 2008). Some studies have suggested that the most common aphasia phenotype of AD is LPA (Gorno-Tempini et al, 2008; Rabinovici et al, 2008; Mesulam et al, 2008), however both PNFA and SD have also been reported, as have syndromes that do not fit clearly into a single category, so-called "mixed" aphasia (Knibb et al, 2006; Alladi et al, 2007). The study described in this Chapter aimed to review the clinical, neuropsychological and cross-sectional neuroimaging features of a retrospective series of fourteen patients with a clinical diagnosis of PPA and AD pathology either demonstrated directly or presumed on the basis of cerebrospinal fluid (CSF) biomarker profile and compare them to previously published series of PPA patients with either pathologically-confirmed AD or a positive PIB-PET scan suggestive of AD.

METHODS

A retrospective review of patients with a diagnosis in the PPA spectrum who had attended the Specialist Cognitive Disorders Clinic, Queen Square, London, UK, and who had donated their brains for post-mortem analysis or who had had a brain biopsy during life was performed. Those who also had either AD pathology at post-mortem/cerebral biopsy were included. In total, 9 patients had pathologically-confirmed Alzheimer's disease (seven who came to post-mortem and two with a cerebral biopsy). Also included in this study were the five patients described in Chapters 5.2 and 5.3 who had CSF biomarker data consistent with Alzheimer pathology (raised CSF total tau level with reduced amyloid Aβ42 fraction: Hulstaert et al, 1999). Clinical notes and neuropsychological data were reviewed in all cases. The clinical diagnosis at the time the patient was assessed and a revised clinical diagnosis based on current

criteria were recorded in each case. Demographic, clinical and pathological data for patients are presented in Table 5.5.1; neuropsychological data are presented in Table 5.5.2.

Brain image acquisition and volumetric measurements were performed as in Chapter 2. The two disease groups and the healthy control group were compared statistically based on contrasts between the group means using a linear regression model in STATA 10.0. Changes in imaging patterns with severity were investigated using cortical reconstruction and thickness estimation methods as described in Chapter 2.3. Performance on the Graded Naming Test (McKenna et al, 1980) (i.e. degree of anomia) was used as a measure of disease severity, splitting the group according to their score: group 1 (moderately anomic: 9 patients) scored > 0 (mean 7.7, standard deviation 9.2) and group 2 (severely anomic: 4 patients) were unable to score. One patient with greater right than left hemisphere atrophy was not included in this analysis. Effect size maps were generated based on the difference in mean thickness in each of these severity subgroups and in the whole group, comparing each to the controls and expressing the disease-control difference as a percentage of the mean control group thickness.

RESULTS

Clinical and neuropsychological features

All patients had language impairment as their primary presenting feature. This was usually difficulty finding words although one patient complained of a return of a childhood stutter shortly before the onset of word-finding difficulties. Spontaneous speech was relatively nonfluent and occasional phonemic errors were made by all patients, with occasional emergence of neologistic jargon errors. None of the patients was described as having had apraxia of speech. All of the patients who came to post-mortem or had a cerebral biopsy had initially received a diagnosis of PPA, PNFA or language variant frontotemporal lobar degeneration although prior to death the diagnosis in two of these cases was changed to atypical language variant of AD. The five patients with CSF biomarkers consistent with AD were ascertained more recently and had been diagnosed with LPA. On review of the clinical notes of the seven patients who came to post-mortem and the two patients with cerebral

biopsy-proven AD, all of those cases would also have met criteria for LPA. A family history of dementia was present in only two cases: these patients each had a single parent with a diagnosis of Alzheimer's disease in the eighth decade. Myoclonus was noted in two patients and two patients developed generalized seizures. One patient exhibited axial rigidity late in the course of the disease; no other features of parkinsonism or motor neurone disease were present in this series. Behavioural impairment was unusual early in the illness but aggression, anxiety and irritability were noted in some patients later in the course.

Neuropsychological assessment showed severely impaired digit span in all but three patients, who scored in the low (but not defective) range. Naming was in the impaired range at initial assessment in over half of the patients and became impaired in all cases as the disease progressed. Single word comprehension was impaired in the more severely affected patients. None of the patients complained of episodic memory impairment at presentation, however verbal memory was impaired in eight of eleven patients tested while visual memory was affected less frequently (five of fourteen patients). Reading was affected in most patients and some were noted to have a phonological dyslexia. Limb apraxia and dyscalculia were noted in most patients however visuospatial skills were intact in all but one severely affected patient. Executive dysfunction was also seen in most patients.

Table 5.5.1

Demographic, symptom and pathology data: shaded cases are patients with CSF data consistent with AD, non-shaded cases are pathologically-confirmed cases

Patient	Age at Onset (years)	Total duration (years)	First symptom	Other linguistic symptoms	Neurological and behavioural symptoms	CSF	Tissue pathology
AD-PPA1	59	9.3	Word-finding difficulty	Phonemic errors, later comprehension problems	Myoclonus and seizures	N/A	Braak VI, CERAD frequent plaques, Reagan high
AD-PPA2	54	8.1	Word-finding difficulty	Phonemic errors, sentence repetition impairment	Seizures	N/A	Braak VI, CERAD frequent plaques, Reagan high.
AD-PPA3	50	6.3	Word-finding difficulty	Phonemic errors	Myoclonus	N/A	Severe pathology frequent plaques and tangles. Extensive amyloid angiopathy.
AD-PPA4	62	5.2	Return of childhood stutter	Word-finding difficulty, phonemic and jargon errors	Nil other noted	N/A	Braak VI, CERAD frequent plaques, Reagan high.
AD-PPA5	66	9.7	Word-finding difficulty	Phonemic errors, sentence repetition impairment	Nil other noted	N/A	Braak VI, CERAD frequent plaques, Reagan high.
AD-PPA6	50	7.2	Word-finding difficulty	Phonemic and jargon errors, later comprehension problems	Later aggressive behaviour	N/A	Braak VI, CERAD frequent plaques, Reagan high.
AD-PPA7	54	8.9	Word-finding difficulty	Phonemic errors	Later axial rigidity Later aggressive	N/A	Braak VI, CERAD frequent plaques, Reagan high.
AD-PPA8	50	N/A	Word-finding difficulty	Phonemic errors	Anxiety	N/A	Cerebral biopsy: Frequent plaques and tangles
AD-PPA9	48	N/A	Word-finding difficulty	Phonemic errors	Nil other notes	N/A	Cerebral biopsy: Frequent plaques and tangles
AD-PPA10	60	N/A	Word-finding difficulty	Phonemic errors	Later anxiety, irritability and disinhibition	tau>1200 ng/l, Aβ42 195 ng/l	N/A

AD-PPA11	53	N/A	Word-finding difficulty	Phonemic errors	Irritability	tau 1146 ng/l , Aβ42 250 ng/l	N/A
AD-PPA12	63	N/A	Word-finding difficulty	Phonemic errors	Anxiety and apathy	tau 1124 ng/l , Aβ42 299 ng/l	N/A
AD-PPA13	59	N/A	Word-finding difficulty	Phonemic errors	Irritability, restlessness and agitation	tau 986 ng/l , Aβ42 138 ng/l	N/A
AD-PPA14	58	N/A	Word-finding difficulty	Phonemic and jargon errors, later comprehension problems	Anxiety	tau 986 ng/l , Aβ42 130 ng/l	N/A

Table 5.5.2

Neuropsychological data

Patient	Duration at assessment	MMSE	VIQ	PIQ	Naming	Single word comprehension	Digit span forwards	Verbal memory	Visual memory	Reading	Limb praxis	Calculation	Visuospatial skills	Executive function
AD-PPA1	4.1	17	61	74	-	-	-	+	+	- (phon)	-	-	+	+
AD-PPA2	3.7	26	83	99	+	+	-	-	+	NT	-	-	+	-
AD-PPA3	2.8	17	66	64	+	+	-	-	+	NT	-	-	+	-
AD-PPA4	3.2	4	Unable	Unable	-	-	-	-	-	- (phon)	-	-	-	-
AD-PPA5	4.0	21	84	68	-	+	+	-	-	+	-	-	+	-
AD-PPA6	3.1	27	79	122	+	+	-	+	+	- (phon)	NT	+	+	+
AD-PPA7	3.1	20	70	107	-	+	-	+	+	-	NT	-	+	+
AD-PPA8	2.3	18	61	79	+	+	-	-	+	+	-	+	+	-
AD-PPA9	2.3	NT	85	91	+	+	-	-	+	-	-	+	+	-
AD-PPA10	5.4	8	NT	NT	-	-	-	NT	+	- (phon)	-	-	+	-
AD-PPA11	3.0	21	79	80	+	+	+	-	-	+	-	-	+	-
AD-PPA12	3.1	17	81	84	-	+	+	-	-	- (phon)	-	-	+	-
AD-PPA13	3.9	16	62	77	-	-	-	NT	+	- (phon)	-	-	+	-
AD-PPA14	4.8	8	NT	NT	-	-	-	NT	-	- (phon)	-	-	+	-

+ represents intact function, - represents impaired function i.e. a score below the 5th percentile on testing; for reading score (phon) represents the presence of a phonological dyslexia; NT = not tested Verbal IQ (VIQ) and Performance (PIQ) scores are taken from the WAIS-R. Verbal and visual memory were tested with the Warrington Recognition Memory Test for Words and Faces, naming with the Graded Naming Test, single word comprehension with the WAIS-R vocabulary subtest or Warrington synonyms test, reading with the National Adult Reading Test or Schonell reading test, visuospatial skills with the Visual Object and Space Perception battery, digit span with the WAIS-R digit span subtest, calculation with the Graded Difficulty Calculation Test (GDCT) and executive function with the Weigl or Wisconsin Modified Card Sorting Tasks or Stroop task.

Pathological features

Six of the seven patients who came to post-mortem had severe Alzheimer pathology with Braak stage VI and CERAD frequent plaques. For the seventh case, no staging information was available but it had been reported as showing severe Alzheimer pathology with frequent plaques and tangles. Four cases were also noted to have cerebral amyloid angiopathy. The two patients who had cerebral biopsies were noted to have frequent amyloid plaques and neurofibrillary tangles.

Neuroimaging features

Volumetric MRI data for patients and an age- and gender matched group of 20 cognitively-normal controls are presented in Table 5.5.3: whole brain and hemisphere volumes were smaller than controls and there was evidence of left/right hemispheric asymmetry at group level and in all but one of the individual patients; one (right-handed) patient showed reverse asymmetry. Asymmetry became more marked with increasing disease duration (Figure 5.5.1, R=0.55, p=0.04).

Table 5.5.3

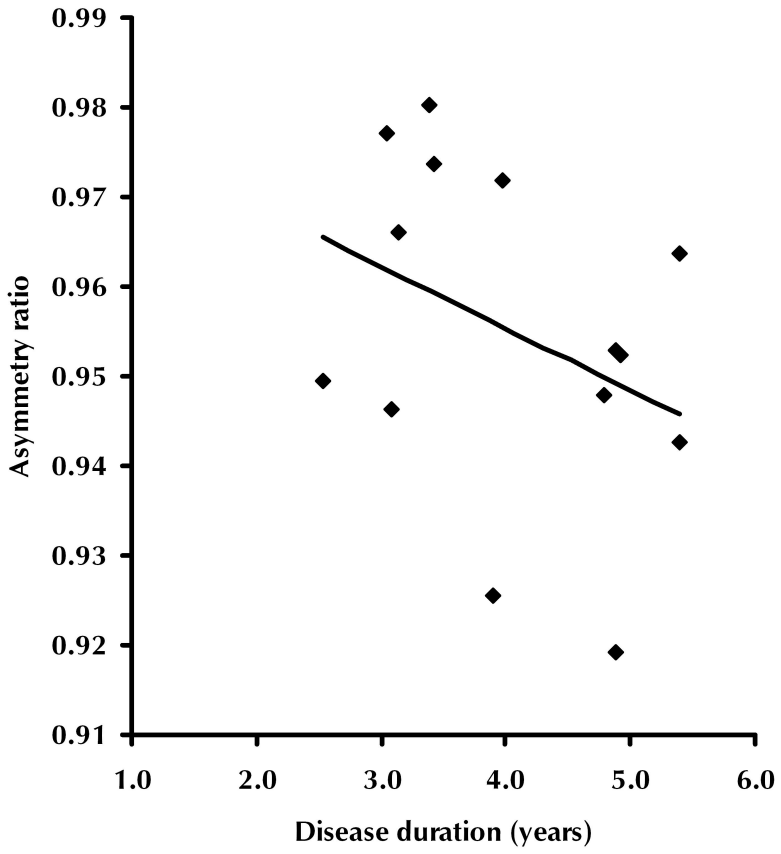
Volumetric cross-sectional data

	Controls	**AD-PPA**
Number of subjects	23	14
Duration of disease at scan	N/A	4.1 (1.0)
Age at baseline scan (years)	63.5 (7.3)	60.2 (6.2)
Brain volume (ml)	1160.1 (96.5)	1083.7 (109.1)[a]
Left hemisphere volume (ml)	570.9 (46.7)	526.4 (57.0)[a]
Right hemisphere volume (ml)	571.3 (46.9)	547.9 (50.6)
Left/right hemisphere ratio	1.00 (0.01)	0.96 (0.03)[a]

[a]p<0.05 AD-PPA significantly worse than controls

Figure 5.5.1

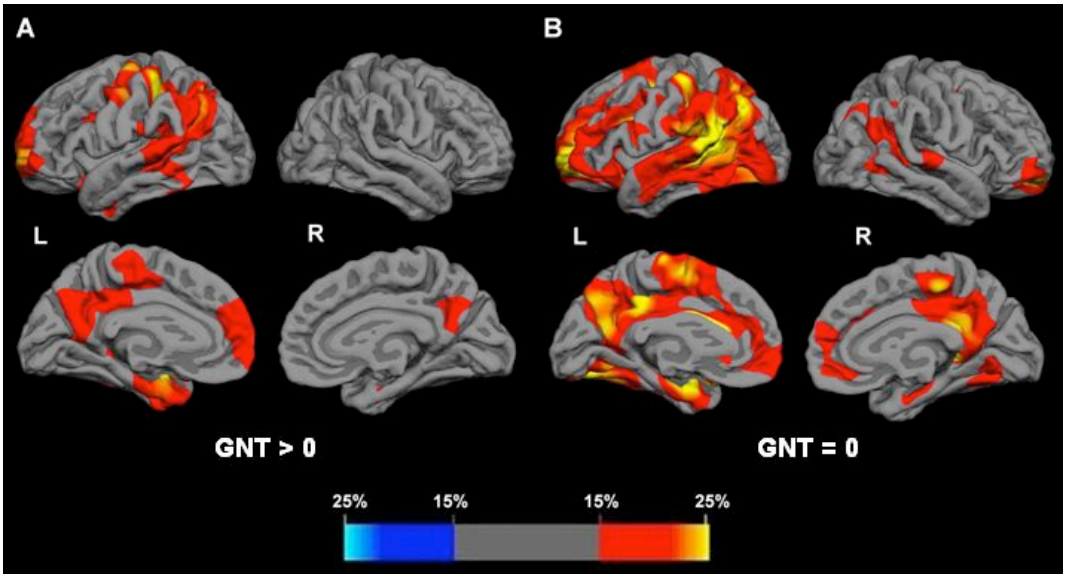
Asymmetry ratio (left:right hemisphere volumes) as a function of disease duration in years



In the cortical thickness analysis versus healthy controls group 1 (with less severe disease) showed areas of cortical thinning predominantly in the left hemisphere, most marked in the inferior parietal and posterior superior temporal lobes (Figure 5.5.2). Other areas involved in the left hemisphere were posterior cingulate, precuneus, medial temporal lobe and prefrontal cortex. In the right hemisphere, only the posterior cingulate and precuneus and a small area in the medial temporal lobe were affected. In group 2 with more severe anomia, cortical thinning remained asymmetrical but was more extensive within both hemispheres. In the left hemisphere there was additional involvement of anterior superior and middle temporal lobe, posterior medial temporal lobe and inferior frontal lobe areas (Figure 5.5.2). In the right hemisphere there was involvement of areas similar to those initially involved in the left hemisphere, i.e. lateral parietal, posterior superior temporal, posterior cingulate, precuneus, medial temporal and prefrontal cortices.

Figure 5.5.2

Patterns of cortical thinning in the AD-PPA groups versus healthy controls, categorized by severity of anomia: group1 (less severe: A), group 2 (most severe: B), For each hemisphere, the top panels are lateral views, the bottom panels medial views. Percentage thinning maps are shown; the coloured bar represents percentage values.



Review of previous cases of PPA with AD pathology

Previous series from five research groups have reported PPA patients with either pathologically-confirmed AD or a positive PIB-PET scan showing amyloid deposition (Galton et al, 2000; Croot et al, 2000; Davies et al, 2005; Kertesz et al, 2005; Knibb et al, 2006; Alladi et al, 2007; Josephs et al, 2008; Mesulam et al, 2008; Gorno-Tempini et al, 2008; Rabinovici et al, 2008; Pereira et al, 2009). Prior to the detailed description of LPA (Gorno-Tempini et al, 2004a), patients with both PNFA and SD were reported with AD pathology but since its recognition LPA has been the clinical syndrome most closely associated with AD pathology: in one series all patients with LPA versus one of six patients with PNFA and one of five patients with SD had positive PIB-PET scans (Rabinovici et al, 2008). It is unclear whether older series included patients that would now be described as having LPA. Some studies of PNFA patients with motor speech deficits (e.g. apraxia of speech) show an association with FTLD-tau rather than AD pathology (Josephs et al, 2006), while a clinical syndrome of SD has been associated chiefly with type 1 TDP rather than AD pathology (Alladi et al, 2007; Snowden et al, 2007).

The SD syndrome underpinned by AD may be associated with asymmetrical temporal lobe atrophy focused on the left hippocampus and superior temporal lobe, rather than the temporal pole and anteroinferior temporal lobe as in classical SD caused by TDP pathology (Pereira et al, 2009; Chan et al, 2001b).

Table 5.5.4

Previously reported series of patients with a primary progressive aphasia and Alzheimer pathology

Series	N with pathologically-confirmed AD	PPA diagnosis	%male	Age at onset	Duration	Age at death
Pereira et al, 2009*	3	3 SD	66.7	NA	NA	NA
Rabinovici et al, 2008^	0 but 6 with positive PIB-PET scan	4 LPA, 1 SD, 1 PNFA	NA	NA	NA	NA
Gorno-Tempini et al, 2008^	0 but 4 with positive PIB-PET scan	4 LPA	25.0	NA	NA	NA
Mesulam et al, 2008	11	7 LPA, 1 SD, 3 “mixed”	63.6	61.8 (10.8)	NA	73.2 (7.0)
Josephs et al, 2008	5	5 "fluent aphasia" ("1 or 2 may meet criteria for logopenic PPA")	60.0	69 (12)	NA	77 (13)
Alladi et al, 2007*	19	12 PNFA, 2 SD, 5 "mixed" (“ mixed” cases include 3 LPA, 2 atypical SD with phonological deficits)	NA	65.7 (8.1)	7.4 (2.9)	NA
Knibb et al, 2006*	12	7 PNFA, 5 SD	NA	NA	NA	NA
Kertesz et al, 2005	8	8 PPA (including PNFA and LPA)	NA	NA	NA	NA

*from same research group and cases may overlap in different series. Note earlier series which include AD-PPA cases are Davies et al, 2005; Croot et al, 2000 and Galton et al, 2000

^from same research group and cases may overlap in different series

NA not available

DISCUSSION

This study describes a series of fourteen patients with PPA in association with proven or probable AD pathology. The key clinical features of the cases in this series were initial presentation with word-finding difficulty, and relatively non-fluent spontaneous speech with occasional phonemic errors but without motor speech impairment. Reviewing the diagnoses in this series revealed that all cases fulfilled (or would likely have fulfilled) descriptive criteria for LPA (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008). The neuropsychological findings of impaired digit span, dyscalculia, limb apraxia and phonological dyslexia were consistent with LPA (Amici et al, 2006; Brambati et al, 2009a). However, verbal memory, although not a presenting feature in any of the patients, was also affected in most cases: this feature has not been emphasised in previous studies of LPA. In contrast, visuospatial processing (a right hemisphere function) was generally well preserved. Cross-sectional brain imaging revealed asymmetrical left-sided atrophy predominantly affecting the posterior superior temporal lobe and inferior parietal lobe but also the posterior cingulate, precuneus and medial temporal lobe: these features corroborate previous neuroanatomical findings in LPA (Gorno-Tempini et al, 2004a; Gorno-Tempini et al, 2008). In more severe disease there was evidence of atrophy spread to the left frontal lobe, more anterior left temporal lobe areas as well as posterior superior temporal lobe, inferior parietal lobe and posterior cingulate areas within the right hemisphere.

The nosology of language impairment with AD pathology remains controversial. Such patients have been classified either as having the clinical/neuropsychological description of PPA (with LPA the most common phenotype) or having the predictive clinico-pathological description of an atypical 'language variant' within the AD spectrum. However, there should not be any conflict between these two descriptions as they are essentially at two different levels of classification. With this said, predicting which patients with a PPA syndrome will have AD pathology is not always easy during life (in the absence of a PIB-PET scan or CSF markers suggestive of AD): while the extent of involvement of other cognitive domains may be helpful, the present evidence suggests that the presence and severity of extra-linguistic impairments depends on disease stage. Furthermore, the clinical salience of these additional impairments is

variable: in this series, a number of patients who performed poorly on episodic memory tasks did not complain of amnestic symptoms, whereas two patients who came to post-mortem exhibited widespread cognitive impairment prompting a reformulation of the clinical diagnosis as an atypical language variant of AD. It seems that the presenting syndrome at early disease stage is likely to provide the more rational basis for classifying language dysfunction associated with AD, particularly as language impairments are very common as 'typical' AD advances. This distinction is clinically important, as recognition of PPA features that predict AD pathology could help direct the use of investigations such as CSF and PIB-PET, and ultimately, the selection of patients for clinical trials and disease-modifying therapies.

An outstanding neurobiological question concerns the overlap of LPA/atypical language-presentation AD with typical amnestic AD (and with other atypical variants of AD such as posterior cortical atrophy). Neuropsychologically, there are few data to compare amnestic-onset AD with atypical language variants but studies of language impairment in typical AD have shown that patients can be logopenic with an early anomia, and that phonological and semantic impairments also occur (Harasty et al, 1999; Harasty et al, 2001; Garrard et al, 2001; Blair et al, 2007; Taler et al, 2008a; Chertkow et al, 2008; Peters et al, 2009). Motor speech impairment (apraxia of speech) has been reported only rarely in association with AD (Gerstner et al, 2007). From an anatomical perspective, LPA is associated with asymmetrical atrophy compared to the relatively symmetrical atrophy of amnestic AD (Gorno-Tempini et al, 2004a). However, certain key areas of atrophy or cortical thinning are implicated in both LPA-AD and typical AD, i.e. the temporo-parietal junction, the precuneus and the medial temporal lobe (Scahill et al, 2002). The present study has certain limitations, including relatively small patient numbers, retrospective ascertainment, and most importantly, lack of uniform histopathological confirmation. Taking these caveats into account, the present evidence in conjunction with previous work suggests that the LPA syndrome might be regarded, very broadly, as a 'uni-hemispheric' presentation of AD: further detailed longitudinal prospective studies comparing amnestic and language presentations of AD are needed in order to elucidate the pathophysiological mechanisms that instigate and sustain neuropsychological and anatomical asymmetry. It will also be useful to investigate the neuropathological findings of a

prospectively studied cohort of patients with detailed neurolinguistic testing to identify associations between pathology and different PPA syndromes.

5.6 Atypical parkinsonian disorders and nonfluent aphasia

The overlap of nonfluent aphasia and corticobasal syndrome (CBS) has been well-described (Graham et al, 2003) but more recently, cases have been reported with a progressive supranuclear palsy (PSP) syndrome. This has both clinical and neurobiological importance: clinically it is important to recognize that a PSP syndrome may later develop in nonfluent aphasia in order to provide useful prognostic information, whilst neurobiologically it is important to study how language impairment develops in what is classically considered a 'subcortical dementia' and how the neuroanatomy of aphasia in PSP compares with other related syndromes. This study aimed to investigate prospectively the clinical, neuropsychological and neuroimaging features of patients presenting with PNFA who subsequently developed characteristic features of PSP. The clinical and neuroanatomical characteristics of these cases were compared with established cases of PNFA without PSP syndrome and with pathologically confirmed classical PSP (Richardson's syndrome, PSP-RS) cases without speech or language impairment.

METHODS

This study was performed subsequently to Chapters 5.2 and 5.3 with fourteen consecutive patients presenting with a clinical syndrome of PNFA investigated.

Clinical assessment

All patients had a structured clinical history, neurological examination, Mini-Mental State Examination (MMSE, Folstein et al, 1975) and Frontal Assessment Battery (FAB, Dubois et al, 2000). Clinical features of a PSP syndrome at presentation or developing subsequently were recorded (Litvan et al, 1996; Litvan et al, 2003): these cases are referred to hereafter as 'PSP-PNFA', while 'PNFA' is used to refer to those cases not developing a PSP syndrome. All patients with clinical features of PSP-PNFA were further assessed using the activities of daily living (part II) and motor (part III) components of the Unified Parkinson's Disease Rating Scale (UPDRS). In addition the severity of any gaze abnormality was assessed (Payan et al, 2002; Blain et al, 2006).

Neuropsychological assessment

A neuropsychological battery with a neurolinguistic focus was administered to all patients and to 14 cognitively-normal control subjects (matched for age and gender; Table 5.6.1). Background neuropsychological tests comprised a general (nonverbal) intelligence test (Raven's Advanced Progressive Matrices, Raven et al, 2003) and tests assessing focal cognitive domains including episodic memory (Camden Pictorial Recognition Memory Test, Warrington, 1996), visuoperceptual skills (the Object Decision subtest of the Visual Object and Space Perception Battery, VOSP, Warrington et al, 1991) and executive function (Trail Making Test, Reitan, 1959). Limb apraxia was assessed as part of the clinical examination.

The neurolinguistic component of the battery assessed a number of key speech and language functions. Spontaneous speech was analysed from a sample obtained by asking subjects to talk about their last holiday and to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination (Goodglass et al, 1983). This sample was recorded and subsequently transcribed and analysed for the number of words produced per minute, number of speech production (i.e. phonemic or phonetic) errors and agrammatic (incorrect tense/plural) errors made per minute and presence and severity of AOS (mild, moderate or severe). Naming was assessed using the Graded Naming Test (McKenna et al, 1980) whilst comprehension was evaluated using the Warrington synonyms test for single words (Warrington et al, 1998) and a shortened version of the PALPA55 test for sentences (Kay et al, 1992). Repetition of mono- and polysyllabic words and sentences was also tested. Reading was assessed using a 30-item irregular word reading test as well as the Graded Nonword Reading Test (Snowling et al, 1996), and spelling was evaluated with the Graded Difficulty Spelling Test (Baxter et al, 1994). Comparisons between the groups were performed using a linear regression model (STATA 10.0).

Brain imaging analysis

All patients and control subjects had volumetric T1-weighted MR brain images as described in Chapter 2. Five patients with pathologically-confirmed PSP-RS without a PNFA syndrome during life who had been imaged on the same scanner with the same MRI volumetric protocol

constituted an additional comparison group. This group comprised four males and one female with a mean age at scan of 68.9 years (standard deviation 4.0). Estimated mean duration from symptom onset was 4.4 (standard deviation 1.3) years. Image analysis was performed as described in Chapter 2 with whole brain volumes measured. Manual segmentation of the midbrain was conducted to determine the midbrain volume (Paviour et al, 2006). Brain and midbrain volumes were expressed as a percentage of the total intracranial volume.

Cortical reconstruction and thickness estimation was performed as described in Chapter 2. A vertex-by-vertex analysis using a general linear model was performed to examine differences in cortical thickness between the disease groups and the control group. Cortical thickness, C, was modelled as a function of group, controlling for age and gender by including them as nuisance covariates. Contrasts of interest between the estimates of the group parameters were assessed using two-tailed t-tests. Maps showing statistically significant differences between the groups were generated and for the comparison with controls, corrected for multiple comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.05 significance level.

Literature review

In order to assess the present series in relation to previously reported cases of PSP with PNFA, a search of the published literature using the MEDLINE internet database (www.ncbi.nlm.nih.gov/sites/entrez/) was conducted and the keywords "PSP", "progressive supranuclear palsy", "gaze palsy", "PNFA", "FTLD", "PPA", "apraxia of speech", "progressive aphasia" and "aphasia", in isolation and in combination. For all papers identified, the clinical details of all cases with pathological confirmation were abstracted. Age at onset, disease duration and age at death were recorded as well as clinical features at presentation and later in the disease course. Whether the cases would meet current research criteria for a diagnosis of PSP (Litvan et al, 2003) was also recorded.

RESULTS

Clinical features

Four of 14 patients presenting with PNFA exhibited clinical features of PSP. Each of these patients had initially developed speech production impairment and only later in the disease course developed features of PSP. Over the same time period two other patients with PNFA developed features of a corticobasal syndrome (Boeve et al, 2003b). The group of PSP-PNFA cases and the group of other PNFA cases were comparable in terms of age, gender, and clinical disease duration (Table 5.6.1). Features of the four PSP-PNFA cases are summarized in Table 5.6.4. In these cases the mean time from onset of language symptoms to development of features of PSP was 4.9 years (range 3.0 to 8.5 years) for gaze palsy and 4.0 years (range 1.0 to 8.0 years) for falls. The patients with PSP-PNFA had mean (standard deviation) scores of 20.0 (6.3) for UPDRS part II and 30.5 (15.8) for UPDRS part III compared to the scores for the five patients with pathologically proven PSP of 18.0 (7.2) for part II and 17.2(7.2) for part III. The four PSP-PNFA subjects had clear supranuclear abnormalities of their eye movements with slow and hypometric vertical and horizontal saccades of similar severity to the cases with pathologically proven PSP.

Neuropsychological assessment

The pattern of neuropsychological and neurolinguistic deficits exhibited by patients with PSP-PNFA was similar to other PNFA patients (Tables 5.6.1 and 5.6.2). On the general neuropsychological assessment (Table 5.6.1), relative to healthy controls both groups had impaired executive function and reduced digit span but intact visuoperceptual skills. The PSP-PNFA group had mildly impaired performance on a recognition memory task, and a higher incidence of limb apraxia than the other PNFA cases. On the detailed neurolinguistic assessment (Table 5.6.2), spontaneous speech analysis was broadly similar in both disease groups. PSP-PNFA and PNFA cases showed similar mean severity of apraxia of speech and number of agrammatic errors. However, the mean overall speech rate (words / minute) was substantially (though non-significantly) lower in the PSP-PNFA group than in the other PNFA cases, while speech production errors were significantly more frequent than healthy controls

only in the PNFA group. Relative to healthy controls, performance on comprehension, repetition and reading tasks was impaired in the PNFA group but not the PSP-PNFA group, however the performance of the two disease groups did not differ significantly. Spelling was significantly more impaired in the PNFA group than the PSP-PNFA group.

Table 5.6.1

Neuropsychological data in patients and healthy controls

	PSP-PNFA	PNFA without PSP	Controls
Number of subjects	4	10	14
%Male	75%	70%	57%
Age (years)	71.2 (5.8)	72.0 (7.4)	69.7 (4.7)
Age at onset (years)	66.0 (6.8)	66.4 (7.9)	N/A
Duration from onset of language symptoms (years)	5.2 (2.5)	5.6 (2.1)	N/A
MMSE score (/30)	26.5 (2.4)	23.0 (6.2)[a]	29.6 (0.9)
FAB score (/18)	8.3 (3.9)[a]	11.0 (4.2)[a]	17.8 (0.4)
Ravens Advanced Matrices IQ	96.3 (23.2)[a]	94.5 (18.5)[a]	113.6 (9.9)
Camden Pictorial Recognition Memory Test (/30)	27.5 (3.0)[a,b]	29.5 (0.8)	29.6 (0.9)
Trail making test A (scaled score)	2.5 (1.6)[a]	4.0 (2.2)[a]	9.7 (2.8)
Trail making test B (scaled score)	4.2 (2.1)[a]	3.7 (3.2)[a]	9.8 (2.8)
VOSP Object Decision (/20)	16.5 (4.5)	16.4 (2.3)	17.1 (2.4)
Limb apraxia (% of cases)	75%	40%	0%
Digit span forwards	5.0 (1.2)[a]	4.7 (1.3)[a]	7.0 (0.6)

[a]$p<0.05$ disease group worse than controls, [b]$p<0.05$ PSP-PNFA worse than PNFA without PSP

Table 5.6.2

Neurolinguistic data in patients and healthy controls

	PSP-PNFA*	PNFA without PSP	Controls
Words/minute	21.0(12.6)[a]	40.3 (18.1)[a]	133.9 (22.9)
Speech production errors/min	0.2 (0.3)	1.5 (1.7)[a]	0.0 (0.0)
Agrammatic errors/min	0.8 (0.1)[a]	0.6 (0.5)[a]	0.0 (0.0)
Apraxia of speech severity (/3)	1.8 (1.0)[a]	1.8 (0.9)[a]	0.0 (0.0)
Naming (/20)	13.5 (9.1)[a]	11.3 (6.4)[a]	19.7 (0.7)
Warrington synonyms test (/50)	40.0 (1.4)[a]	38.1 (6.9)[a]	48.6 (1.3)
Modified PALPA 55 test (/24)	20.0 (13.5)[a]	19.2 (4.3)[a]	23.4 (0.9)
Single word repetition (/30)	22.5 (15.0)	22.0 (10.8)[a]	29.8 (0.4)
Sentence repetition (/10)	6.8 (4.6)	5.3 (4.6)[a]	10.0 (0.0)
Irregular word reading test (/30)	20.0 (13.5)	15.2 (8.1)[a]	28.0 (1.8)
Graded difficulty nonword reading test (/20)	11.3 (8.4)[a]	8.1 (5.7)[a]	19.6 (0.7)
Graded difficulty spelling test (/30)	24.7 (3.2)	7.6 (7.8)[a,b]	25.6 (2.8)

[a]$p<0.05$ disease group worse than controls, [b]$p<0.05$ PNFA without PSP worse than PSP-PNFA

*One PSP-PNFA case was mute at the time of assessment

Brain imaging analysis (Table 5.6.3 and Figures 5.6.1 and 5.6.2)

Mean total brain volume as a percentage of intracranial volume was significantly smaller than controls only in the PNFA group. Mean midbrain volume was smaller than controls in the PSP-PNFA and PSP-RS groups. Mean midbrain volume in the PSP-PNFA group was significantly smaller than the PNFA group but significantly larger than the PSP-RS group (Table 5.6.3).

Table 5.6.3

Brain volumetric data in patients, controls and a pathologically-confirmed group of patients with classical PSP (PSP-RS)

	PSP-PNFA (n=4)	PNFA without PSP (n=10)	PSP-RS (n=5)	Controls (n=14)
Brain volume (% of TIV)	65.2 (5.9)	62.1 (4.9)[a]	65.4 (4.1)	69.4 (4.2)
Midbrain volume (% of TIV)	4.2 (0.5)[a,b]	5.2 (1.0)	3.1 (0.5)[a,c,d]	5.3 (0.6)

[a]p<0.05 disease group smaller than controls, [b]p<0.05 PSP-PNFA smaller than PNFA without PSP, [c]p<0.05 PSP (RS) smaller than PSP-PNFA v, [d]p<0.05 PSP (RS) smaller than PNFA without PSP

Cortical thickness maps showed a characteristic pattern of predominantly left hemispheric atrophy in the PNFA group compared to the control group with most significant thinning of inferior frontal and superior temporal cortices (Figure 5.6.1A). The PSP-PNFA group had significant cortical thinning mainly in the left inferior and superior frontal lobe (Figure 5.6.1B). There were no significant areas of cortical thinning in the PSP-RS group compared to controls. There were no significant differences in cortical thickness between any of the disease groups when compared directly and corrected for multiple comparisons. Uncorrected significance maps and percentage thickness difference maps between groups are shown in Figure 5.6.2: cortical thickness was reduced in bilateral prefrontal areas in PSP-PNFA compared to PNFA (blue areas in Figure 5.6.2A); in a more extensive network of predominantly left-sided and mainly prefrontal areas in PSP-PNFA versus PSP-RS (blue areas in Figure 5.6.2B); and in superior and mid-temporal and posterior peri-Sylvian areas in PNFA versus PSP-PNFA (red/yellow areas in Figure 5.6.2A); there were no significant areas (at an uncorrected level of p=0.05) of cortical thinning in PSP-RS versus PSP-PNFA (Figure 5.6.2B).

Figure 5.6.1

Cortical thickness maps showing patterns of cortical thinning in disease groups (yellow/red) compared to controls (blue): A) PNFA without PSP and B) PSP-PNFA. No significant areas of thinning were seen in a comparison of PSP-RS and controls. Left hemisphere is shown above, right hemisphere below; for each hemisphere, the top panels are lateral views, the bottom panels medial views. Coloured bar represents FDR corrected p-values.

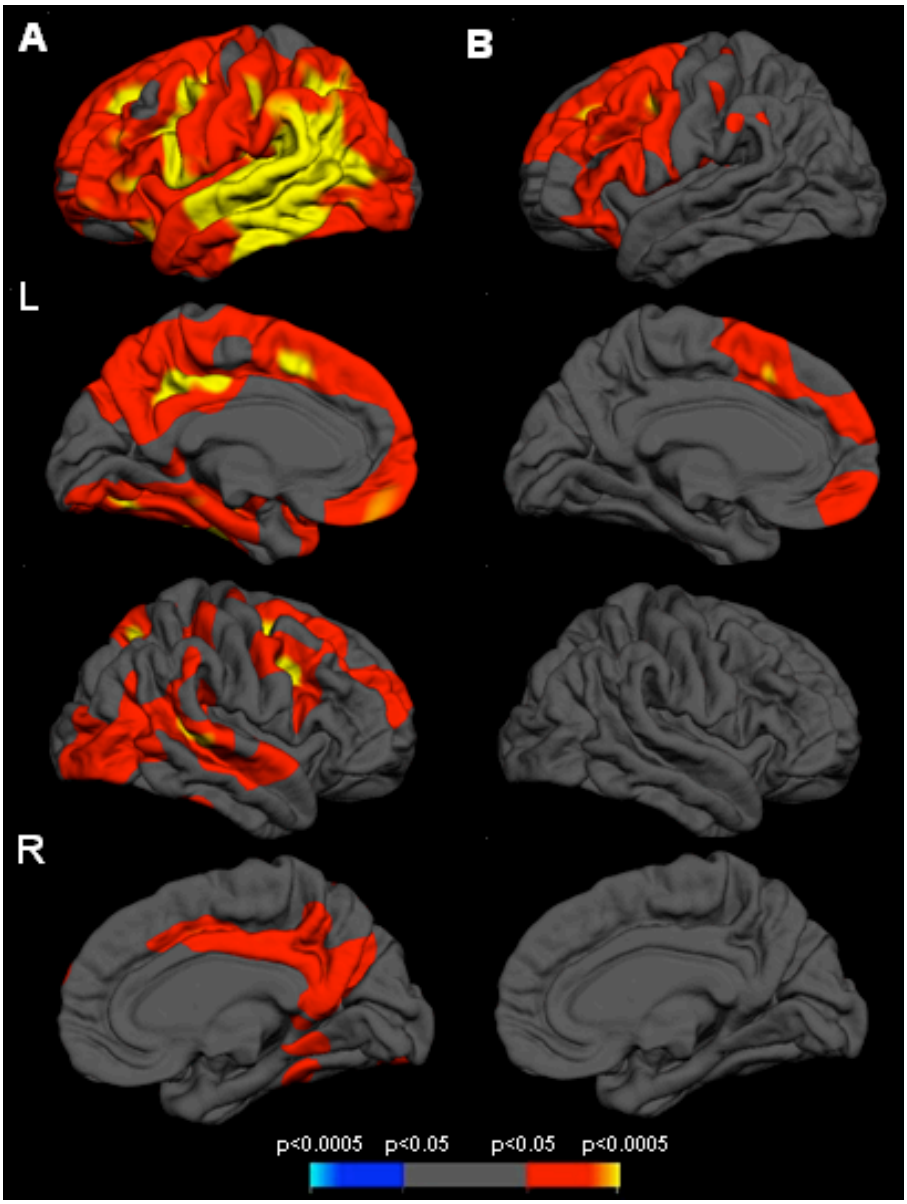
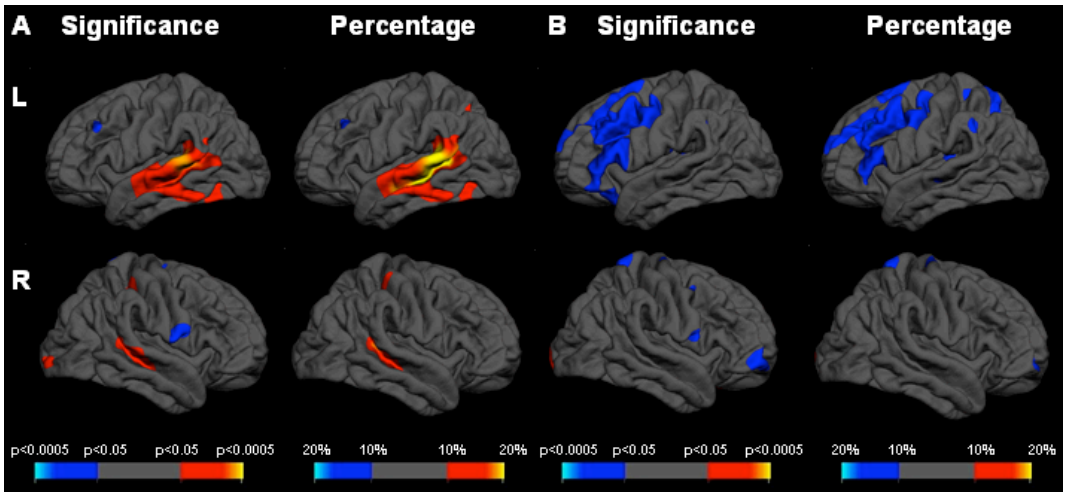


Figure 5.6.2

Cortical thickness maps showing patterns of cortical thinning in disease comparisons: A) PNFA without PSP (yellow/red) versus PSP-PNFA (blue) and B) PSP-PNFA (blue) versus PSP-RS. Left hemisphere is shown above, right hemisphere below with lateral views shown. Left sided pictures represent significance maps with coloured bar representing uncorrected p-values; right-sided maps represent percentage thinning maps with coloured bar representing a percentage value.



Summary of published literature

A total of 12 cases of PSP presenting with a speech production disorder from seven separate studies were identified (Table 5.6.4: Boeve et al, 2003; Josephs et al, 2005; Josephs et al, 2006; Karnik et al, 2006; Mochizuki et al, 2003; Wakabayashi et al, 2000; Perkin et al, 1978). The diagnosis during life in these cases was most commonly recorded as PNFA, nonfluent dysphasia, PPA or AOS. Ten of the 12 cases were examined at post mortem and five classified as having typical PSP pathology. Atypical PSP pathology, or combinations of pathological abnormalities with PSP as the predominant diagnosis were identified in the five remaining cases (Table 5.6.4). The age at onset, disease duration and age at death of these cases did not differ significantly from other phenotypes of pathologically-proven PSP (classical PSP or Richardson's syndrome, PSP-RS, PSP-Parkinsonism or PSP-P and pure akinesia with gait freezing or PAGF: data from Williams et al, 2005; Williams et al, 2007) (Table 5.6.5). However disease duration was closer to the classical PSP phenotype (RS) than to PSP-P or PAGF.

Table 5.6.4

Cases with PSP and speech production impairment (PSP = progressive supranuclear palsy, PPA = primary progressive aphasia, PNFA = progressive non-fluent aphasia, AOS = apraxia of speech, NA = not available, NK = not known, OCD = obsessive compulsive disorder. ∗cases not already described in previous publication by the same authors. ∗ - not pathologically proven)

Author *Nomenclature*	N	Age at onset (years)	Symptoms/Signs at onset	Gaze palsy (duration from onset - years)	Falls (duration from onset - years)	Duration to death (years)	Other symptoms and signs during disease course	Pathological diagnosis
This series *PNFA*	4	67	Articulatory difficulty: hesitant, effortful speech, confusion between yes and no	+ (3)	+ (3)	NK	Mild limb bradykinesia and rigidity, limb apraxia	NK
		73	Speech production impairment with word-finding difficulty and hesitancy	+ (3)	+ (1)	NK	Apathy, depression	NK
		65	Articulatory difficulty with effortfulness and word-finding difficulty. Loss of ability to hum or whistle.	+ (8.5)	+ (8)	NK	Mild parkinsonian syndrome, with right limb myoclonus and limb apraxia	NK
		57	Decreased speech amount with hesitancy and effortfulness in speech production	+ (5)	+ (4)	NK	Limb apraxia	NK
Wakabayashi *et al.* *PPA*	1	72	"Aphemia", decreased speech output	-	NA	6	No other early signs. Late right hemisphere (temporal/occipital) stroke.	PSP
Boeve *et al.* *PNFA*	1	71	Anomia, AOS.	-	+ (5-6)	6	Mild Parkinsonism, agitation.	Atypical PSP Amyloid angiopathy
Josephs *et al.* *AOS* *PNFA*	4	77	Naming difficulty and non-fluent speech.	+ (2)	+ (3)	5	Mild asymmetric spasticity, axial rigidity.	Atypical PSP Hippocampal sclerosis Braak stage I
		53	Articulatory difficulty, AOS, emotional lability.	-	-	8	Late obsessional behaviour, brisk reflexes.	Atypical PSP Braak stage III
		69	Difficulty with pronunciation, confusion between yes/no.	+ (4)	-	8	Head tremor, brisk reflexes. Family history of motor neuron disease and dementia.	Atypical PSP Braak stage IV-V Transitional LB
		70	Anomia, hesitancy, paragrammatic errors, AOS.	-	-	7	Mild hypomimia, late behavioural problems.	Atypical PSP Amyloid angiopathy
Josephs *et al.* *Progressive aphasia/AOS∗*	2	69	AOS.	+ (NA)	-	9	Limb apraxia, rigidity and bradykinesia.	PSP
		74	AOS.	-	-	8	Limb apraxia, rigidity and bradykinesia.	PSP
Karnik *et al.* *PNFA*	1	62	Apathy, anhedonia, worsening depression, effortful non-fluent speech	-	+ (2)	4	Severe OCD since aged 40yrs, falls in context of post surgical foot drop.	PSP

Mochizuki *et al.* *PPA*	1	64	Difficulty with spontaneous speech on the telephone.	-	+ (10)	10	Right upper limb clumsiness, brisk reflexes. Repetitive behaviour.	PSP
Perkin *et al.* *PSP with dysphasia*	2	57	Speech production difficulties	NA	NA	NK	Right upper limb tremor and rigidity	NK
		58	Non-fluent dysphasia	NA	NA	NK	Right upper limb rigidity	NK

Table 5.6.5

Comparison of age of onset, disease duration and age at death in the different PSP phenotypes (based on data from Table 2 and previous studies of classical PSP (PSP-RS) and PSP-P)

	Clinical presentation	Age at onset	Disease duration	Age at death
PSP-PNFA	Difficulty with speech production	64.9 (7.2)	6.7 (2.0)	73.8 (7.0)
PSP-RS	Gaze palsy, axial rigidity and falls	66.5 (7.4)	6.3 (2.4)	72.8 (7.1)
PSP-P	Asymmetric tremor, late falls and gaze palsy	63.2 (9.9)	11.7 (4.9)	74.9 (9.3)
PAGF	Gradual onset of freezing of gait	61 (age range 44-78)	13 (age range 5-21)	Not available

DISCUSSION

This study characterises the syndrome of progressive nonfluent aphasia/apraxia of speech with clinical features of PSP. The neuropsychological and neurolinguistic profile of PSP-PNFA is similar to PNFA (Table 5.6.1 and 5.6.2), consistent with the extensively overlapping pattern of cortical atrophy in these two syndromes (Figure 5.6.1). However, the syndromes do differ in certain respects: compared with PNFA, PSP-PNFA is associated with more profound reduction in spontaneous speech, and more prominent deficits of praxis and episodic memory, but fewer speech errors and less marked impairment of literacy skills. This pattern of clinical and cognitive deficits in PSP-PNFA is consistent with the relatively greater involvement of prefrontal areas and less marked involvement of temporal and posterior perisylvian areas visualised in the cortical thickness analysis of the PSP-PNFA cases. However, it is noteworthy that more severe midbrain atrophy was observed in the PSP-PNFA group than the PNFA-only group: midbrain atrophy here is likely to represent a marker for more extensive involvement of basal ganglia and other subcortical structures in PSP-PNFA. Lesions of subcortical nuclei can themselves give rise to a range of neuropsychological deficits (Warren et al, 2000). Furthermore, pathological examination in cases of PSP with progressive aphasia/apraxia of speech has demonstrated grey matter atrophy predominantly affecting the superior premotor cortex spreading to the bank of

the precentral gyrus and supplemental motor area and other frontal regions, as well as the caudate nuclei and the globus pallidus (Josephs et al, 2006). Considering these lines of evidence together, it is therefore plausible that a conjunction of cortical and subcortical damage determines the neuropsychological profile in PSP-PNFA.

Though subject to ascertainment bias, the present study suggests a prevalence of PSP-PNFA of the order of 29% of all cases of PNFA. Although our cases have not been pathologically confirmed, they share a number of clinical and neuroradiological similarities with pathologically proven cases in the PSP spectrum. A review of the presenting clinical features of the 170 cases of pathologically-confirmed PSP in the Queen Square Brain Bank database revealed four cases with speech or language problems at presentation although no detailed clinical assessments were available on these patients. These retrospective data suggest an approximate prevalence of PSP-PNFA of at least 2% of all pathologically-confirmed PSP: this is likely to be an underestimate, due to incomplete data recording and ascertainment bias (the majority of cases were recruited and assessed via a specialist movement disorders clinic). Previous work has demonstrated that diseases in the FTLD spectrum may show evolution of the clinical phenotype over the course of the illness: patients may present with a particular syndrome, and subsequently develop features of another syndrome. In one series of 60 patients with FTLD (Kertesz et al, 2005), 22 initially presented with PPA: of these 9 developed features suggestive of PSP/CBS during the course of the disease, however none had specific PSP pathology at post mortem. One case presenting as typical PSP clinically developed progressive aphasia as a late manifestation and was found to have histopathological features of PSP. Taken together with the evidence of previous cases of speech-led presentations of pathologically proven PSP (Table 4.6.4), it is possible that progressive aphasia is more commonly underpinned by PSP pathology than is widely recognised. On the other hand, a proportion of these cases have 'atypical' features histopathologically, and the role of such anomalies in modifying the clinical phenotype has not been defined. There are several potential sources of bias in work of this kind. Patients presenting with progressive aphasia may not undergo comprehensive general neurological examination later in the illness, patients with PNFA in whom clinical features of PSP rapidly supervene may be less frequently included in

pathological series of FTLD cases, while patients with classical PSP who develop speech or language deficits later in the illness may not have detailed neuropsychological assessment. Conversely, it is unclear what proportion of 'typical' PNFA cases may have 'subclinical' features of the PSP syndrome: this would entail a detailed (longitudinal) analysis of oculomotor function in all patients presenting with PNFA, which was not undertaken here. These observations further underline the need for detailed longitudinal studies with pathological correlation in patients presenting with PNFA and PSP.

Taking these caveats into account, the present study suggests the existence of a fourth clinico-anatomical variant of PSP, in line with previous calls for greater recognition of this syndrome. The PSP-PNFA syndrome is of both clinical and neurobiological importance. Clinically, the patient with progressive speech apraxia and early marked impoverishment of propositional speech without prominent speech errors should be observed closely for development of the PSP syndrome. Neurobiologically, such cases suggest that PSP should no longer be regarded as a paradigmatic 'subcortical' dementia: rather (analogously with other neurodegenerative disorders, such as dementia with Lewy bodies and corticobasal degeneration) it represents a spectrum of overlapping syndromes that may have a cortical emphasis at presentation.

Chapter 5 summary

This Chapter has looked at a prospective series of patients with progressive language impairment. The clinical and anatomical syndromes seen in patients with semantic dementia in this series are as previously described, all presenting with verbal semantic impairment and all in this study with left greater than right temporal lobe atrophy. The novel aspects of this Chapter rest upon the descriptions of the nonfluent aphasia variants – there is preliminary evidence from the neurological, neuropsychological, neuroanatomical, genetic and pathological evidence presented here that there are at least three nonfluent PPA syndromes:

- The PNFA syndrome, where apraxia of speech is an early feature but patients develop agrammatism over time. This is associated clinically with atypical parkinsonian syndromes, either corticobasal syndrome or progressive supranuclear palsy. Previous studies and the work presented in Chapter 4 suggest that these clinical syndromes (CBS and PSP) are usually associated with tau-positive pathology.
- The LPA syndrome, where word-finding pauses are prominent as is a short-term (phonological) memory deficit. However, this study suggests that this syndrome is far more complex cognitively than previously described: other cognitive domains involved, particularly as the disease develops, are likely to include phonological code retrieval, verbal memory impairment and semantic processing. The CSF data and the review of the pathological series suggest a strong association with Alzheimer's disease pathology as with previous reports. The imaging in these cases, which is asymmetric, mainly affecting the left hemisphere, suggests that LPA is a focal variant of AD initially affecting the left hemisphere rather than symmetrically as seen in typical amnestic AD. As discussed in Chapter 1, it is important to be clear on the descriptive levels of classification when discussing this syndrome – it is not inconsistent to call this syndrome either logopenic/phonological aphasia (i.e. a clinical/neuropsychological classification) or an atypical language presentation of Alzheimer's disease (i.e. a clinico-pathological classification).
- A *GRN*-PPA syndrome, associated with progranulin mutations, where anomia is a prominent initial feature and there is nonfluency secondary to anomia with relatively mild agrammatism but with early semantic impairment. This study has only looked at a small

number of these patients and whilst it is uncontroversial that this is a separate pathogenetic PPA syndrome, the prediction that this forms a separate clinical/neuropsychological phenotype that maps directly on to the pathogenetics remains to be answered with larger studies.

It will be important to conduct further group and detailed single case studies in patients with nonfluent aphasias and particularly those with pathological confirmation to define the full clinico-pathological and clinico-genetic spectrum, to establish the extent to which *GRN*-PPA, LPA and other nonfluent cases can be distinguished on neuropsychological grounds (or whether they represent one instance of a broader continuum of non-fluent aphasia cases with different molecular substrates), and to address in detail the anatomical and pathophysiological basis of the different language disorders.

6. Further neuropsychological and behavioural studies

As described in the previous Chapters, patients with PPA have a wide variety of speech and language deficits that differ between the subtypes: anomia and impaired single word comprehension secondary to a verbal semantic deficit in SD; agrammatism, motor speech impairment, anomia and impaired repetition in PNFA; and anomia and impaired sentence repetition and comprehension in LPA. Consistent with this, both structural and functional MRI studies have shown involvement of a distributed left hemisphere fronto-temporo-parietal language network in PPA (Sonty et al, 2003; Vandenbulcke et al, 2005; Sonty et al, 2007). Following on from the work in the prospective series of patients with PPA described in Chapter 5, individual studies addressing particular neuropsychological and behavioural aspects of patients with progressive aphasias are presented in this Chapter: studies of single word processing (6.1), prosody (6.2), the production of neologistic jargon (6.3), apraxia (6.4) and abnormal behaviour (6.5) are presented, all areas which have been little studied in most cases in the progressive aphasias previously.

The specific hypotheses of Chapter 6 are:

1. Impairment of single word processing in the progressive aphasias will be associated with a network of areas in the left hemisphere.
2. Prosodic processing will be impaired in patients with nonfluent aphasias.
3. Orofacial and limb apraxia will be associated with nonfluent aphasia and limb apraxia will be particularly associated with the atypical parkinsonian disorders, corticobasal syndrome and progressive supranuclear palsty syndrome.
4. Behavioural abnormalities will occur in progressive aphasias particularly with increased disease severity and the pattern of abnormalities will differ across the different clinical subtypes.

6.1 Single word processing in primary progressive aphasia

Single word processing is thought to rely upon widespread neural networks within the dominant hemisphere (Price, 2000; Martin, 2003). Historically, study of these cognitive processes has relied upon discrete lesions in patients with neurological deficits such as stroke and tumours (Dronkers et al, 2004; Hillis, 2007) although in recent years this has been supplemented with an array of functional MRI experiments mostly in cognitively-normal individuals (Fiez et al, 1998; Price 2000; Bookheimer, 2002; Martin, 2003; Demonet et al, 2005; Vigneau et al, 2006). More recently, diffusion tractography has been used as a method of identifying white matter tracts involved in language (Breier et al, 2008; Friederici, 2009). Fewer studies have looked at neurodegenerative disease as a model for investigating single word processes such as naming, comprehension and reading.

During the early stages of the disease all of the progressive aphasias have naming deficits with anomia more marked in SD than LPA and relatively mild impairment in PNFA. VBM studies suggest that overlapping but distinct areas of the language network correlate with anomia (Galton et al, 2001; Grossman et al, 2004; McMillan et al, 2004; Amici et al, 2007): in SD anomia is associated mostly with anterior temporal lobe atrophy, whilst in PNFA a more widespread network of areas is associated with anomia, particularly inferior frontal, lateral temporal and anterior parietal lobes. Single word comprehension/semantic impairment in SD is associated with anterior temporal lobe atrophy (Davies et al, 2004; Nestor et al, 2006; Davies et al, 2008). The development of single word comprehension deficits in both LPA and PNFA has not been studied in detail and the underlying cognitive domains involved remain unclear. Reading deficits differ between the subtypes: surface dyslexia is seen in SD (i.e. inability to read irregular or exception words) and in an fMRI study a group of SD patients (unlike cognitively-normal controls) did not activate anterior temporal lobe areas thought to be required for exception word reading but instead activated a left inferior parietal area not seen in normal individuals (which may explain the regularization of exception words that SD patients commonly exhibit) (Wilson et al, 2009a). Phonological dyslexia is seen in PNFA and LPA i.e. particular difficulty reading nonsense or pseudowords, and is associated in PPA with left temporo-parietal atrophy (Brambati et al, 2009a).

In this study single word processing (naming, comprehension and reading) was investigated in the group of 32 patients with PPA and volumetric imaging described in Chapters 5.2 and 5.3 using the unbiased whole brain technique of voxel-based morphometry in order to look at the neuroanatomical correlates.

METHODS

The 32 patients (14 PNFA, 9 SD, 7 LPA, 2 *GRN*-PPA) had been tested on a various measures of single word processing as described in Chapter 2.2 and 5.2: 1) a 20-item oral picture naming task, 2) two tests of single word comprehension; A) a purely verbal single word comprehension task, the Warrington synonyms task which consists of 25 concrete words and 25 abstract words (Warrington et al, 1998); and B) a verbal-visual single word comprehension task, a shortened version of the word-picture matching British Picture Vocabulary Scale; and 3) a single word reading task consisting of 30 irregular words (i.e. mainly sampling vocabulary-based reading). Results in each of the tests from the different groups are shown in Table 6.1.1. Naming and verbal comprehension were similarly impaired in the SD and LPA groups (and more impaired than PNFA) with the worst performance in the *GRN*-PPA group. The SD group were worse than both LPA and PNFA on the visual-verbal comprehension task with similar performance to the *GRN*-PPA group. Reading was most severely affected in *GRN*-PPA and least affected in PNFA.

Table 6.1.1

Demographic and neuropsychological data

	ALL PPA	***SD***	***PNFA***	***GRN*-PPA**	**LPA**
Age (years)	67.0 (8.6)	*62.3 (9.0)*	*71.8 (6.8)*	*60.7 (12.7)*	*65.1 (6.4)*
Number of subjects	32	*9*	*14*	*2*	*7*
Gender (M:F)	18:14	*3:6*	*10:4*	*1:1*	*4:3*
Duration (years)	5.0 (1.7)	*5.3 (1.2)*	*5.3 (2.1)*	*3.7 (0.0)*	*4.4 (1.0)*
Naming (/20)	7.9 (6.6)	*4.4 (3.2)*	*12.7 (6.4)*	*0.0 (0.0)*	*5.1 (4.2)*
Verbal comprehension (/50)	33.9 (7.5)	*28.9 (5.3)*	*39.9 96.7)*	*26.0 (0.0)*	*30.7 (2.4)*
Visual-verbal comprehension (/30)	21.0 (6.0)	*15.1 (5.2)*	*25.4 (4.0)*	*15.5 (2.1)*	*21.1 (2.7)*
Reading (/20)	15.5 (8.3)	*15.4 (8.3)*	*18.1 (8.6)*	*4.5 (0.7)*	*13.4 (6.6)*

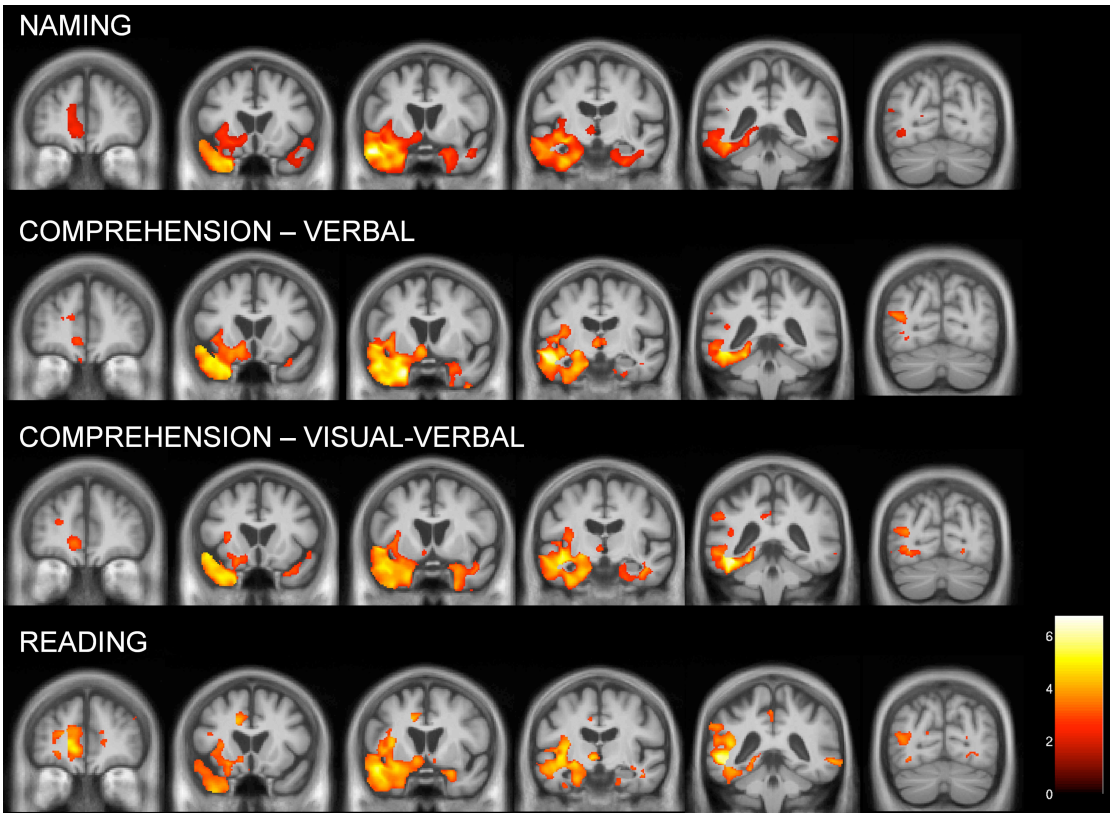
The results from these four tests were used to investigate the neuroanatomical basis of single word processing by correlating score on the tests with grey matter intensity on T1 MRI brain scans using voxel-based morphometry (VBM). VBM was performed using SPM5 software with default settings for all parameters as described in Chapter 2. Linear regression models were used to examine correlations between psychological test score and grey matter intensity. Voxel intensity was modelled as a function of score in each of the four tests (within the same model) with group membership (i.e. SD, PNFA, LPA or *GRN*-PPA), subject age and total intracranial volume (TIV) included as nuisance covariates. Maps showing statistically significant correlations between score and voxel intensity were generated, correcting for multiple comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.05 significance level (Figures 6.1.1 and 6.1.2). Statistical parametric maps were displayed as overlays on a study-specific template, created by warping all native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

RESULTS

A similar network of mainly left-sided grey matter areas correlated with the naming, comprehension and reading scores: temporal lobe, insula, inferior frontal lobe, inferior parietal lobe and anterior cingulate (Figure 6.1.1). For naming the most significant areas were in the left anterior temporal lobe [-51, 5, -21; -33, 0, -17; -28, -6, -32] and more posterior middle temporal [-51, -22, -16] and superior temporal [-40, -9, -10] lobes within the same hemisphere with significant right anterior temporal [24, -1, -33] involvement also. There was less significant involvement of the left anterior cingulate [-7, 39, -3], insula [-34, 1, 3], inferior frontal lobe [-36, 27, 1] and inferior parietal lobe [-45, -44, 22]. Verbal comprehension involved a similar network of areas with anterior temporal lobe [-36, 20, 18] being most significant. For the visual-verbal comprehension task there was also particularly significant correlation with the posterior inferior temporal lobe [-38, -43, -12] and there was more right temporal lobe [25, 3, -30; 40, -18, -15] involvement than the purely verbal comprehension task. Reading was associated with the same network of areas but in contrast to the naming and comprehension was most significantly associated with grey matter atrophy in the middle and superior temporal gyrus posteriorly [-50, -36, 1; -45, -24, -3; -45, -39, -5].

Figure 6.1.1

VBM analysis correlating grey matter with scores on the naming, comprehension and reading tasks in the PPA cohort. Statistical parametric maps (SPMs) have been thresholded at p<0.05 (FDR corrected) and rendered on a study-specific average group T1-weighted MRI template image in DARTEL space. The colour bar (right) indicates the t score. The right hemisphere is shown on the right side of the image in the coronal sections.



DISCUSSION

This study describes an overlapping network of mainly left hemisphere areas associated with single word processing in primary progressive aphasia. In particular, common cortical areas affected were in the temporal lobe (particularly the pole and the posterior superior and middle temporal gyri), posterior inferior frontal gyrus, insula, inferior parietal and anterior cingulate lobes.

Naming from a picture relies on a number of cognitive processes including semantic knowledge of the concept in the picture, linking the semantic concept to the word, retrieving

the word from the lexicon, and then expressing the word (Indefrey et al, 2004; Grossman et al, 2004; Patterson et al, 2007). A widely spread network of cortical areas is therefore predicted to be associated with this process as is seen in this study: semantic areas such as anterior temporal lobe, posterior superior temporal lobe, areas involved in speech production such as the insula and association areas such as inferior parietal lobe. As with naming, single word comprehension requires knowledge of the semantic concepts involved in the task but also involves phonological decoding of syllables. In a purely verbal task, it is mainly the key semantic areas of the left hemisphere involved but with a visual component to the task there is also greater involvement of the right hemisphere consistent with this hemisphere's involvement in visual semantic knowledge (Pobric et al, 2009). The ability to read an irregularly spelled word requires prior knowledge of the word and is therefore likely to rely on similar semantic and lexical areas as naming and comprehension tasks. In this study, similar grey matter regions to the other tasks correlated with reading score although more posterior temporal areas were most significant which may signify the major requirement of lexical access in this task.

One of the difficulties of studying a heterogeneous group of patients where the underlying pathological causes may be different is the validity of combining such such patients. It may be that different pathologies have differential effects on grey matter volume e.g. some may cause impaired function without volume loss compared with others which cause substantial volume loss. Caution must therefore be taken in the results from any study with mixed pathological groups.

The ability to study patterns of language impairment in degenerative disease and its neuroanatomical correlations has potential advantages over other methods. Degenerative disease tends to affect areas of the brain substantially different to strokes e.g. anterior temporal lobe. This area of the brain is also more susceptible to artefact in fMRI studies with semantic task studies often showing more superior and posterior temporal involvement and inferior frontal lobe rather than anterior temporal lobe involvement (Vigneau et al, 2006).

6.2 Receptive prosody in nonfluent aphasia

Whereas the production and processing of verbal material in PPA has been extensively studied, less attention has been paid to nonverbal aspects of vocal communication. Expressive prosody, or the 'melody' of speech, is abnormal in many patients with PPA (Josephs et al, 2006): apraxia of speech or expressive agrammatism in PNFA, and word-finding pauses in LPA tend to disrupt the rhythm and intonational structure of utterances, rendering them dysprosodic. However, it is not clear whether such patients have an underlying deficit in the comprehension of prosody, 'receptive dysprosodia' (Ross, 1981). This issue is of both neurobiological and clinical importance: neurobiologically, such a deficit would signify a pervasive derangement in the processing of vocal signals in PPA, while clinically, there would be important implications for everyday communication. Prosody is complex and conveys multidimensional information about the speaker's intentions and emotional state, while allowing disambiguation of the meaning of an utterance (e.g. statement versus question). At the most fundamental acoustic level, prosody comprehension depends on an ability to process variations in vocal pitch, duration and intensity (loudness) that constitute the building blocks of prosodic contours. Higher-order processing of intonational patterns is required to determine lexical stress and declarative versus interrogative intention (linguistic prosody), and representation of affective information is required to decode the speaker's emotional state (affective prosody).

In this study a systematic investigation of different dimensions of prosody processing (acoustic, linguistic and affective) was conducted in a cohort of patients with PPA versus healthy older control subjects. Voxel based morphometry was used to identify neuroanatomical correlates of prosodic functions in the PPA group.

METHODS

Nineteen consecutive patients with a diagnosis of PNFA (n = 11), LPA (n = 5), *GRN*-PPA (n=3) and 14 cognitively-normal control subjects were recruited. This study was performed subsequently to those in Chapter 5 and so whilst there is some overlap in the patients, they are not equivalent. One patient (with LPA) had known mild industrial hearing loss; peripheral

hearing was assessed in relation to age norms using pure tone audiometry in 17 patients, and subclinical peripheral hearing loss involving speech frequencies (below 4000 Hz) was detected in a further two cases (both with PNFA). All patients had an initial general neuropsychological assessment including tests of single word comprehension (the Warrington synonyms test, Warrington et al, 1998), executive function (Trail Making Test, Reitan, 1959) and a forwards digit span. Demographic and neuropsychological data are summarised in Table 6.2.1: the PPA group performed significantly worse than controls on all tests, while the only significant difference between the PNFA and LPA subgroups was more impaired single word comprehension in LPA. All patients underwent MR brain imaging as described in Chapter 2.

Table 6.2.1

Demographic and neuropsychological data

	ALL PPA	***PNFA***	***LPA***	***GRN-PPA***	**Controls**
Number of subjects	19	*11*	*5*	3	14
Age (years)	68.6 (7.9)	*72.8 (6.5)*	*63.1 (4.4)*	*62.0 (8.5)*	68.2 (4.8)
Gender (M:F)	12:7	*7:4*	*3:2*	*2:1*	7:7
Duration (years)	4.9 (1.6)	*5.3 (1.9)*	*4.5 (1.0)*	*4.3 (0.6)*	N/A
Warrington synonyms test (/50)	36.2 (1.5)	*39.6 (1.8)*	*31.4 (2.4)*	*31.7 (6.7)*	48.0 (0.3)
Trail making test A (scaled score)	3.8 (0.6)	*2.9 (0.4)*	*5.7 (4.0)*	*4.2 (2.7)*	10.1 (0.5)
Trail making test B (scaled score)	3.0 (0.5)	*3.1 (0.5)*	*2.0 (0.8)*	*4.5 (4.8)*	10.7 (0.5)
Digit span forwards	4.1 (0.3)	*4.4 (0.4)*	*4.6 (1.5)*	*2.0 (1.0)*	6.9 (0.1)

All subjects were assessed using a battery of tests probing different aspects of receptive prosody. All stimuli were prepared or recorded as digital wavefiles from a notebook computer. AKG K141 Monitor headphones were used at comfortable listening level in a quiet room. Several practice trials were given for each test, to ensure subjects understood the task; no feedback was given about performance during the test.

Experiment 1 Acoustic processing of prosody components

The structure of the experimental tasks is schematised in Figure 6.2.1.

A) Pair Discrimination (PD) task (12 trials)

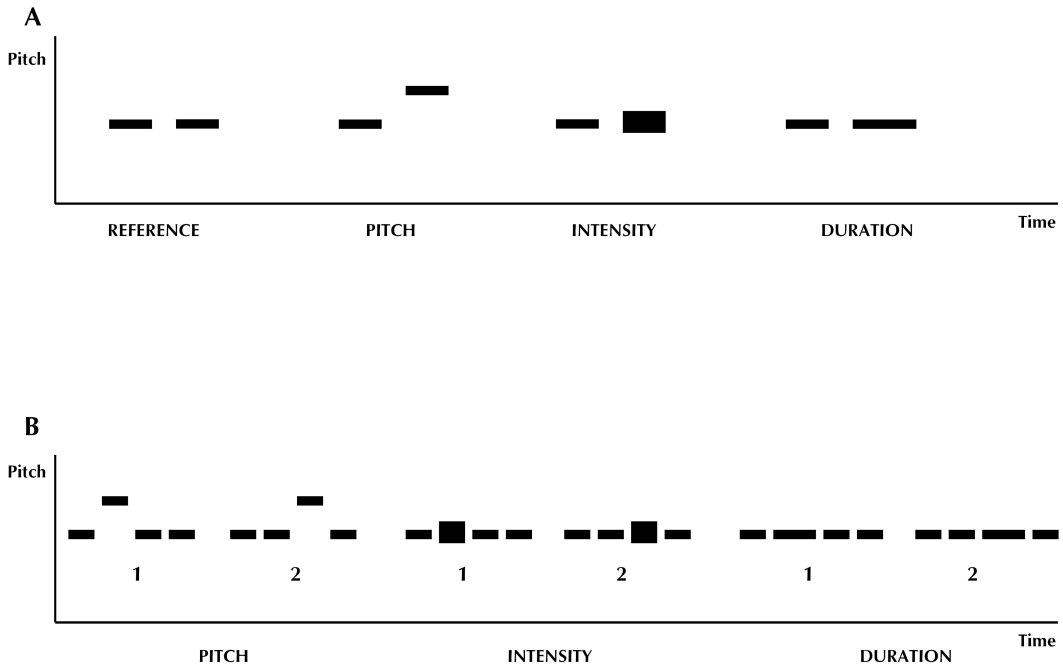
Subjects were presented with pairs of CV syllables (e.g., 'ma'). On half the trials, syllables contained a single difference in pitch, intensity or duration; on the remaining trials the syllables were acoustically identical. Stimulus parameters were digitally manipulated using Matlab7.0© (www.mathworks.com); pitch was manipulated using a previously described algorithm (von Kriegstein et al, 2006). The prosody variations used were intended to be easily detectable by normal subjects (see Figure 1 legend for stimulus parameters). The task on each trial was to decide whether the two sounds were the same or different (i.e., a 'match' versus 'non-match' design).

B) Contour Discrimination (CD) task (match/nonmatch, 12 trials)

Subjects were presented with pairs of short (4-item) sequences of CV syllables as in (A), where each sequence in the pair contained a change in pitch, intensity or duration (parameters as in (A)), but this change could occur at either of two positions (position 2 or 3) with equal probability. The task was to decide whether the two prosodic (pitch, intensity or duration) contours in each pair were the same or different.

Figure 6.2.1

Diagram showing the design of task 1, testing the acoustic processing of prosodic components: A) pair discrimination subjects heard either a pair of syllables of same pitch, duration and intensity or two pairs of differing pitch, intensity (represented by thicker rectangle) or duration; and B) contour discrimination subjects heard two 4-syllable sequences (1 and 2, in either order) for either pitch, intensity or duration and were asked to say whether same or different.



Experiment 2 Linguistic prosody

A) Stress Discrimination (SD) task (2 alternative forced choice, 14 trials)

Subjects heard a spoken phrase of the type: '**black** and blue' [stressed word in bold] and were asked to decide whether the first or second colour in the phrase was stressed.

B) Intonation Discrimination (ID) task (2 alternative forced choice, 14 trials)

Subjects heard a two-syllable word (name of a food) spoken either declaratively or interrogatively (e.g. 'apple' vs. 'apple?'). The subject's task was to decide whether what they heard was a statement (as if read from a list) or a question (as if they were being asked if they wanted the food).

Experiment 3 Emotional (affective) prosody (6 alternative forced choice, 24 trials)

This experiment was adapted from Sauter (PhD thesis, 2006), based on a previously normed set of vocal emotional stimuli. Subjects heard a semantically neutral three digit number (e.g. 'one hundred and forty-seven') recorded by an actor and spoken to convey one of six basic emotions (happiness, surprise, fear, sadness, disgust, anger; the set of sounds representing 'happiness' were spoken to convey either amusement or achievement). For each of the six emotions, four trials representing that emotion were administered; stimuli that were most consistently identified as representing that vocal emotion by the previous group of healthy control subjects (Sauter, PhD thesis, 2006) were selected. The task on each trial was to decide which of these emotions was represented.

Behavioural analysis

Behavioural data were analysed statistically using STATA 10.0 (Stata Corporation, College Station, TX). Linear regression models were used to compare performance on the tests between groups after adjusting for age. 95% bias-corrected bootstrap confidence intervals with 1000 replicates were used. To look at within disease group comparisons Wilcoxon signed-rank tests were used to assess differences between patient scores as a percentage of the control mean.

RESULTS

Behavioural data

On the acoustic processing and linguistic prosody tests, the LPA subgroup performed significantly worse than controls on all tests (Table 6.2.2). The PNFA and *GRN*-PPA subgroups were significantly worse than controls on all tests apart from stress discrimination (Table 6.2.2). The LPA group performed significantly worse than the PNFA group on the pair and intonation discrimination subtests, and worse than the *GRN*-PPA group on the pair and stress discrimination subtests. For the PPA group as a whole, performance was significantly worse on contour discrimination compared to pair discrimination (p=0.02) and on intonation discrimination compared to stress discrimination (p=0.002); there was a significant correlation

between the total acoustic processing score and linguistic prosody score (r=0.50, p=0.03). The three patients with peripheral hearing deficits performed within the range of performance of patients without hearing deficits, suggesting that prosodic deficits were not attributable simply to peripheral hearing loss. No prosody subtest score correlated with auditory short term memory capacity, as indexed by digit span, in any of the subgroups.

On the emotional prosody test, the PNFA subgroup performed significantly worse than controls in total and on each of the individual emotions (Table 6.2.2). The LPA subgroup performed significantly worse than controls in total and on each of the individual emotions except surprise where there was a trend to worse performance. The small GRN-PPA did not perform significantly worse than controls on any of the emotions although there was a trend to worse performance on each of the emotions. There was no significant difference between the subgroups on any of the individual emotions. For the PPA cohort overall, sadness and surprise were best recognised and disgust and fear least well recognised; there were statistically significant differences in recognition performance for fear versus surprise (p=0.03) and sadness (p=0.02) and for disgust versus surprise (p=0.046). The qualitative pattern of recognition performance for individual emotions was similar in patients and healthy controls (Table 6.2.2).

Table 6.2.2

Acoustic processing, linguistic prosody and emotional prosody data

	ALL PPA	*PNFA*	*LPA*	*GRN-PPA*	Controls
Acoustic processing					
Pair discrimination (/12)	9.3 (1.6)*	*9.5 (1.8)**	*8.2 (1.1)*,a,b*	*10.0 (1.0)**	11.4 (0.7)
Contour discrimination (/12)	7.8 (2.5)*	*7.5 (2.9)**	*7.8 (2.6)**	*9.0 (0.0)**	11.5 (0.5)
TOTAL(/24)	17.1(3.4)*	*17.0 (3.8)**	*16.0 (3.5)**	*19.0 (1.0)**	22.9 (1.0)
Linguistic prosody					
Stress discrimination (/14)	12.1 (2.6)*	*12.5 (1.8)*	*10.2 (3.8)*,b*	*14.0 (0.0)*	13.9 (0.5)
Intonation discrimination (/14)	9.1 (2.5)*	*9.6 (2.9)**	*8.0 (2.2)*,a*	*9.0 (1.0)**	13.4 (1.0)
TOTAL(/28)	21.2 (4.0)*	*22.1 (4.0)**	*18.2 (3.8)*,a,b*	*23.0 (1.0)**	27.2 (1.4)
Emotional prosody					
Sadness (%)	65.8 (32.5)*	*75.0 (29.6)**	*55.0 (27.4)**	*50.0 (50.0)*	98.2 (6.7)
Surprise (%)	60.5 (29.2)*	*61.4 (30.3)**	*55.0 (37.1)*	*66.7 (14.4)*	91.1 (15.8)
Anger (%)	46.1 (35.6)*	*50.0 (40.3)**	*40.0 (28.5)**	*41.7 (38.2)*	85.7 (16.2)
Happiness (%)	44.7 (24.4)*	*40.9 (23.1)**	*45.0 (32.6)**	*58.3 (14.4)*	80.4 (20.0)
Disgust (%)	31.6 (23.3)*	*38.6 (20.5)**	*15.0 (13.7)**	*33.3 (38.2)*	64.3 (25.4)
Fear (%)	30.3 (27.1)*	*31.8 (22.6)**	*20.0 (32.6)**	*41.7 (38.2)*	78.6 (29.2)
TOTAL (/24)	11.1 (3.7)*	*11.8 (2.9)**	*9.2 (2.8)**	*11.7 (7.1)*	19.9 (2.6)

*p<0.05 disease group worse than controls , [a]p<0.05 LPA worse than PNFA, [b]p<0.05 LPA worse than *GRN*-PPA

DISCUSSION

This study has demonstrated impairments of receptive prosody in nonfluent PPA syndromes. Deficits were exhibited for acoustic, linguistic and affective dimensions of prosodic analysis. The finding of impairment even at the level of the basic acoustic building blocks of prosodic contours and the correlation between acoustic and linguistic prosody performance argue for the involvement of early perceptual mechanisms that cascade to higher levels of prosodic processing in PPA. Whereas prosodic variation in syllables and words typically extends over tens to hundreds of milliseconds, prosodic contours typically extend over hundreds to thousands of milliseconds: the prosodic subtests used here (syllable pairs/word stress versus contour/intonation) might index the processing of prosodic structure over shorter versus longer

timescales, respectively. Contour discrimination was significantly more impaired than pair discrimination and intonation discrimination was significantly more impaired than stress discrimination at phrasal level: this pattern suggests that the representation of longer range prosodic structure is relatively more vulnerable. While this pattern might be at least partly attributable to an associated short term memory impairment, the lack of correlation between prosodic and short term memory performance argues for an additional specific deficit of receptive prosody.

Within the domain of affective prosody, recognition of certain emotions (in particular, disgust and fear) was relatively more impaired. The pattern observed would be consistent with a primary defect of perceptual analysis: whereas emotions such as sadness and surprise can be conveyed vocally from relatively coarse perceptual cues (e.g., large shifts in intensity or pitch), the perception of vocal expressions of other negative emotions is likely to depend on accurate encoding of fine-grained perceptual features (Juslin et al, 2003; Hammerschmidt et al, 2007). Healthy subjects may be able to exploit additional acoustic features of affective prosodic utterances, or alternatively, there may be an additional specific deficit in processing particular vocal emotions in PPA: the present data do not resolve this issue.

Perception of prosody has been little studied in degenerative disease. Impairments of affective prosody processing have been documented in Huntington's disease (Speedie et al, 1990), Parkinson's disease (Dara et al, 2008), Alzheimer's disease (Taler et al, 2008a) and frontotemporal dementia (right temporal lobe atrophy: Perry et al, 2001). The brain basis for prosodic deficts in these disorders remains largely unexplored. Studies of prosody in patients with stroke or fMRI studies in cognitively-normal individuals have implicated a predominantly right-sided (though often bilateral) distributed fronto-temporo-parietal network in the processing of emotional prosody, with less consistent lateralisation for the processing of linguistic prosody (e.g. Tong et al, 2005; Ethofer et al, 2006; Pell, 2006a; Pell, 2006b; Wildgruber et al, 2006; Beaucousin et al, 2007; Arciuli et al, 2007; Wiethoff et al, 2008; Ross et al, 2008). Speech prosody serves a key 'metalinguistic' function in human communication, and deficits of prosody processing therefore have potentially important clinical consequences.

Indeed, as PPA typically affects the left hemisphere initially, receptive dysprosodia may become more clinically significant with increasing right hemisphere involvement as the disease evolves. This may also be the reason for worse performance in the LPA group which was shown to have greater right hemisphere involvement than the other groups in Chapter 5. Further longitudinal studies with larger PPA cohorts are needed to establish the natural history of prosody impairment in PPA in relation to linguistic deficits, to explore other aspects of complex sound processing across the PPA spectrum and to define the brain basis of prosodic deficits in detail.

6.3 Neologistic jargon in primary progressive aphasia

The production of incomprehensible language containing frequent phonemic distortions, semantic errors or neologisms secondary to neurological disease has been termed jargon aphasia (or if writing is affected, jargon agraphia). The production of inappropriate language can be considered in the context of either normal propositional speech or writing, or in the production of single words in the context of naming tasks performed during neuropsychological assessment. Three types of jargon aphasia have been described (Alajouanine, 1956; Perecman et al, 1985): the production of language which is devoid of content and consists of real words that are inappropriate given the context of the situation (*semantic jargon*); the production of language containing inappropriate words that are nonetheless phonemically-related to what the patient is attempting to convey, and may therefore be either real or non-existent words (*phonemic or phonological jargon*); and the production of language containing non-existent words or true neologisms, which are not phonemically-related to the target (*neologistic jargon*). Patients may have one or more of these types of jargon as part of the same disorder. The occurrence of true 'abstruse' neologisms is most common in acute neurological disorders and in particular Wernicke's aphasia.

Analogously, jargon agraphia can comprise semantic jargon, phonological jargon (phonologically-related misspelled words which can be either real words or nonwords) and neologistic jargon (Cappa et al, 1987; Schonauer et al, 1994; Marien et al, 2001; Marshall, 2006). Jargon aphasia and agraphia can occur in the same individual but they can also occur in the presence of normal output in the other language channel (Schonaeur et al, 1994; Hillis et al, 1999). They are rarely described in the setting of neurodegenerative disease (Ostberg et al, 2001; Graham et al, 2001). Two cases of neologistic jargon in primary progressive aphasia (PPA) are described: jargon aphasia in a case of atypical semantic dementia (SD) and jargon agraphia in a case of progressive non-fluent aphasia (PNFA).

CASE REPORTS

Case 1

A 75 year-old right-handed woman presented with a three-year history of word-finding difficulties. Her husband had noticed she would frequently use 'thing' in place of a more specific word and would confuse words of related meaning (such as 'door' for 'window'). For the previous two years she had also had increased difficulties with arithmetic, writing and spelling. Over the same time period her comprehension of speech had also deteriorated. There had been no significant difficulties with episodic memory and she had never become lost. There were no behavioural symptoms or changes in appetite. There was no family history of dementia. When first assessed she had a fluent aphasia with circumlocutory speech. Repetition for single words was preserved but sentence repetition was impaired. There was bilateral limb apraxia. The general neurological examination was normal. Detailed neuropsychological assessment revealed severe anomia (only able to produce 'train' on a simple naming task) and impaired comprehension (13/50 on the British Picture Vocabulary Scale, Dunn et al, 1982), poor reading skills (2/50 on the National Adult Reading Test, Nelson, 1991) with errors for both irregular and nonwords as well as evidence of parietal dysfunction consisting of dyscalculia (0/24 on the Graded Difficulty Calculation Test, Jackson et al, 1986), poor spelling and decreased digit span (four digits forwards, unable to repeat two digits backwards.). There was also evidence of executive dysfunction

Over the next year the patient's speech became more circumlocutory and with increased word-finding difficulties. In addition, abstruse neologisms emerged in her spontaneous speech and she produced neologistic jargon on a simple naming task and when reading (see Table 6.3.1). She would produce words that were completely unrelated to the target word (e.g., 'adepgood' for 'spade'). At a further assessment seven months later she continued to produce multiple abstruse neologisms (Table 6.3.1). She showed no awareness of the errors she made.

Table 6.3.1

Simple picture naming task and spoken responses from Case 1 (International Phonetic Alphabet characters in parentheses; Response 1 at 4 years after onset)

	TARGET	RESPONSE 1	RESPONSE 2 (+7 months)
1	**Lobster**	Delkwai (dɛlkwɑɪ)	Joon (dʒuːn)
2	**Tricycle**	Doopid (duːpɪd)	Pekakis (pɛkækɪs)
3	**Spade**	Adepgood (ædɛpgʊd)	Haygis (heɪgɪs)
4	**Owl**	Baybeeay (beɪbiːeɪ)	Veeches (viːtʃɛz)
5	**Violin**	Atepown (eɪtpaʊn)	Joh (jəʊ)
6	**Hippopotamus**	Six twenty	Beeap (biːæp)

It is difficult to characterise the syndromic diagnosis in this patient. Based on the leading features of fluent, empty speech with profound anomia, loss of word meaning, impaired single word comprehension and surface dyslexia, the case fulfilled modified consensus criteria for SD (Neary et al, 1998; Adlam et al, 2006). However, the early development of dominant parietal lobe deficits (dyscalculia, limb apraxia and decreased digit span) are clearly atypical for SD, and suggest that the syndrome here might be more appropriately characterised as LPA although the early single word comprehension abnormalities would be against this.

Brain imaging

The patient had volumetric brain MRI scans (Figure 6.3.1A) 3.5 and 5 years from symptom onset i.e. pre and post the onset of jargon. Visual inspection of the baseline scan revealed asymmetrical atrophy affecting predominantly the left cerebral hemisphere and, in particular, the temporal lobe and, to a lesser extent, the parietal lobe. There was no antero-posterior gradient of atrophy within the temporal lobe and the superior, middle and inferior temporal lobe gyri were all affected. There was no vascular disease. The pattern of regional atrophy progression between the two scans (i.e. over the period when jargon developed) was assessed using a fluid registration technique producing a voxel compression map as described in Chapter 2. This showed that progressive atrophy was maximal in the left temporal and inferior

parietal lobes (see figure 6.3.1A), with additional heavy involvement of dorsal prefrontal areas that are likely to be functionally connected with the inferior parietal lobe (Warren et al, 2005).

Case 2

A 70-year-old right-handed man presented with an eighteen month history of progressive speech production impairment. There were no other cognitive or behavioural symptoms. When first assessed he had a non-fluent aphasia with phonemic paraphasias, agrammatism and poor polysyllabic word and sentence repetition. He also had evidence of a mild motor speech disturbance with hesitancy and effortfulness in articulation. The Mini-Mental State Examination score (Folstein et al, 1975) was 25/30 with points lost on naming, writing and registration. The general neurological examination was normal. There was no family history of degenerative disease. EEG performed at this time showed excess slow wave activity in the left frontotemporal region but there was preserved alpha rhythm.

Detailed neuropsychological assessment at presentation revealed a verbal IQ of 77 and a performance IQ of 148 on the WAIS-R (Wechsler, 1981). Despite the speech production impairment naming was relatively intact at this time scoring between the 75th and 90th percentile on the Graded Naming Test (McKenna et al, 1980). There was evidence of mild executive dysfunction (Modified Card Sorting Test, Nelson, 1976), mild to moderate impairment of calculation (Graded Difficulty Calculation Test) and decreased digit span (four digits forwards). However, single word comprehension was intact (50-75th percentile on the Synonyms test, Warrington et al, 1998) as was memory (25th percentile on the Warrington Recognition Memory Test for Words and 75th on the Faces subtest, Warrington, 1984). Visuoperceptual skills were also intact (18/20 on the Object Decision subtest of the VOSP, Warrington et al, 1991).

Over the next two years the patient's speech production continued to deteriorate and he developed difficulties with speech comprehension. In order to communicate he would write things down but there were frequent grammatical and spelling errors. There was also evidence of impaired calculation although no behavioural abnormalities. When assessed three and a half

years after the onset of symptoms there was little spontaneous speech output beyond 'yes' and 'no'. There was evidence of orofacial apraxia although no limb apraxia. Neuropsychological assessment at this time revealed a Raven's matrices equivalent IQ score of 120, intact memory (50-75th percentile on the Camden Pictorial Memory Test, Warrington, 1996) and intact visuoperceptual skills (75-100th percentile on the Object Decision subtest of the VOSP). There was executive dysfunction as previously. In addition there was now evidence of deterioration in single word comprehension, scoring only at the 10th to 25th percentile on the Synonyms test. There was profound anomia: on the Graded Naming Test he was only able to provide written answers to the test (Table 6.3.2) with multiple phonological (e.g., 'squeezers' for 'tweezers') and semantic (e.g., 'elephant' for 'anteater') errors and evidence of perseveration. On a further writing task he was asked to construct sentences containing a target word: he produced grossly agrammatic and often nonsensical phrases containing semantic errors, though no neologisms.

When assessed one year later he was almost mute. Speech comprehension had further deteriorated, now scoring below the 5th percentile on the Synonyms test. Written responses to the Graded Naming Test (Table 6.3.2) contained phonological (e.g., 'rudii' for 'radius'), semantic (e.g., 'hood' for 'cowl') and perseverative errors as previously. However, these were now accompanied by multiple abstruse neologisms completely unrelated to the target word (e.g. 'magiff' for 'sporran', 'gatyss' for 'centaur'). He appeared unaware of these errors. He was assessed once more when completely mute a further year later when he scored 8/20 on a subset of the British Picture Vocabulary Scale (Dunn et al, 1982): although this score is above chance it falls below the 5th percentile. Once again there were multiple abstruse neologisms on the Graded Naming Test with frequent perseverations and illegal letter combinations (e.g. in the neologism IN-KINJCK) (Table 6.3.2).

Table 6.3.2

Written answers provided for the Graded Naming Test from Case 2 (Response 1 at 3.5 years after onset)

	TARGET	RESPONSE 1	RESPONSE 2 (+1 year)	RESPONSE 3 (+2 years)
1	**Kangaroo**	KANGAROO	KANGOROO	GOWN
2	**Scarecrow**	SCARECROWS	BREAKFAST	NECKOR
3	**Buoy**	BOUYS	BOUY	ABOUT
4	**Thimble**	THIMBLE	THUMB	NEXT
5	**Handcuffs**	HANDCUFFS	HANDCUFF	NEWT-NOCKET
6	**Tweezers**	SQUEEZERS	FISTCUFF	NEWBOT
7	**Corkscrew**	CORKSCREWS	SQUIDELL	NEWBOT
8	**Sporran**	KILTS	MAGIFF	NEWBOLT
9	**Tassel**	TASSLE	GNOME	NEWBOLT
10	**Sundial**	TIMESCALE	GNOME	NEWBOLT-BRINE
11	**Chopsticks**	CROQUETS	FORSTELL	NEWBOLT
12	**Periscope**	PERISCOPE	PERSPIME	SINKS-TRINKET
13	**Boar**	BOARS	BOAR	BASIN-MISSKIKIET
14	**Blinkers**	BASKETS	SQUID	BINSTASS
15	**Monocle**	MONCLE	BONECULE	SINKS
16	**Turtle**	TORTOISE	TORQUISE	TRINS-MASSINESS
17	**Trampoline**	TAMPTOISE	BONECULE	MISSKITEN
18	**Bellows**	BELLOWS	FIREBALL	NISS-EN
19	**Shuttlecock**	TAMBLECOCKS	COCKELL	MISS-IN-TEKEN
20	**Anteater**	ELEPHANTS	*No written response*	MISS-IN-TAKIN
21	**Pagoda**	PELICANS	*No written response*	IN-TAKIN
22	**Radius**	RADIUS	RUDII	NO-NOKEN
23	**Leotard**	COSTUME	CATUSS	IN-TOKEN-NO
24	**Mitre**	MITRE	MITRE	IN TOKEN-MOTOKEN
25	**Yashmak**	MASKS	SHIEL	JUINK-
26	**Sextant**	SEXTENTS	SEXTENT	IN-JUNK
27	**Centaur**	M	GATYSS	IN-KINJCK
28	**Cowl**	HOODS	HOOD	IN JUINK-INJUINK
29	**Tutu**	FLUFFS	BAYSONNE	IN JUINK-BOSMENT
30	**Retort**	GLASS	*No written response*	JACKOO

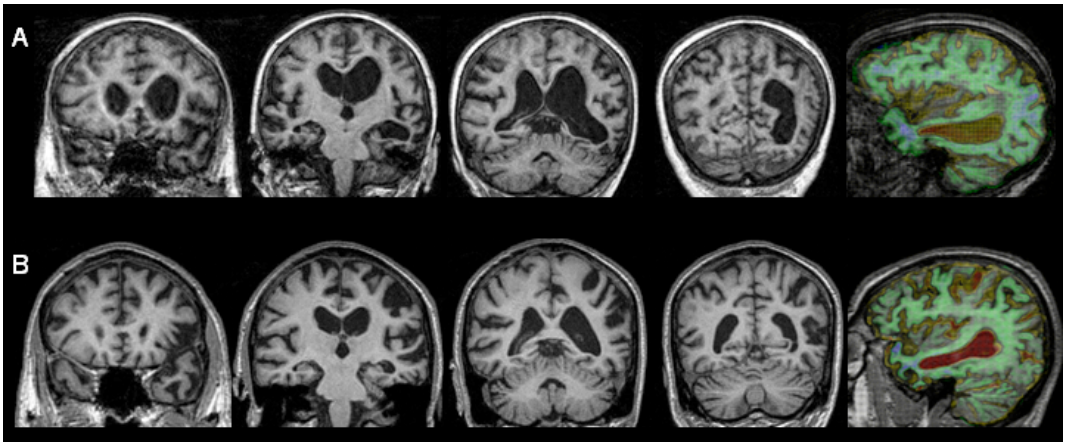
As in Case 1, the syndromic diagnosis in this patient is not clear-cut. Based on the leading features of speech production impairment with agrammatism, sound errors and hesitancy, the clinical presentation here fulfilled consensus criteria for PNFA (Neary et al, 1998). However, other features, in particular the presence of parietal lobe deficits (dyscalculia, decreased digit span) at presentation would be relatively against this.

Brain imaging

The patient had volumetric brain MRI scans (Figure 6.3.1B) 3.5 and 4.5 years from symptom onset, i.e. pre and post the onset of jargon. Visual inspection revealed asymmetrical cerebral atrophy more marked on the left and particularly involving the inferior frontal gyrus and peri-Sylvian region, with extension into the left parietal lobe. There was no vascular disease. As with case 1, the pattern of regional atrophy progression between the two scans (i.e. over the period when jargon developed) was assessed using a fluid registration technique (figure 6.3.1B). This showed progressive atrophy extending posteriorly surrounding the Sylvian fissure with major involvement of the left inferior parietal lobe, in particular the angular gyrus (see figure 6.3.1B).

Figure 6.3.1

Coronal T1-weighted MR images (with left hemisphere shown on the right of the images) through the frontal, mid-temporal, posterior temporo-parietal and posterior parietal regions and a sagittal MR image through the left temporo-parietal region with a voxel-compression-mapping overlay to show the progression of regional atrophy (degree of volume loss and expansion coded in the colour scale: red represents 20% or greater expansion of voxels and blue represents 20% or greater contraction of voxels.): A) Case 1: coronal images 5 years after symptom onset; sagittal image shows change over time period 3.5 to 5 years from symptom onset B) Case 2: coronal images 4.5 years after symptom onset; sagittal image shows change over time period 3.5 to 4.5 years from symptom onset



DISCUSSION

Both patients described here developed neologistic jargon in the context of a neurodegenerative disease with a progressive aphasia phenotype. It is of interest to consider why jargon may have developed in these cases. While neologisms are common in aphasias resulting from acute focal brain damage (in particular strokes affecting the posterior superior temporal–inferior parietal region), neologistic jargon has rarely been reported in neurodegenerative disease (Ostberg et al, 2001; Graham et al, 2001). In particular, it is not mentioned in consensus criteria for frontotemporal lobar degeneration (FTLD) subtypes including PPA nor in recent reviews of PPA or FTLD (Grossman et al, 2004; Hodges et al, 2007). The speech of patients with SD often consists of empty, circumlocutory phrases somewhat similar to those produced by patients with stroke aphasias such as transcortical sensory aphasia or Wernicke's aphasia (Jefferies et al, 2006b), however neologisms are rarely

reported. One previously described case of SD studied late in the disease course exhibited nonword production on a verbal fluency task although spontaneous neologisms were not described (Jefferies et al, 2006b). Neologisms are rarely described as a feature of PNFA or LPA. Both cases here had a clinical syndrome of PPA with additional features that would be atypical for FTLD yet would not fulfil alternative diagnostic categorisations such as Alzheimer's disease (AD). Although Case 1 had clear evidence of severe semantic memory impairment there were also early clinical features of dominant parietal lobe impairment which would not be typical of SD. Moreover, findings on brain imaging were not typical for SD (Chan et al, 2001b) in that there was no anteroposterior gradient of atrophy in the temporal lobes, the left superior temporal gyrus was severely involved, and atrophy extended posteriorly to involve the left parietal lobe. Case 2 had a diagnosis of PNFA, presenting with classical features of non-fluent speech, agrammatism, phonemic paraphasias and impaired polysyllabic word repetition. Of note, as well as asymmetrical left-sided predominant temporal lobe atrophy, he also had early involvement of the dominant inferior parietal lobe both clinically (dyscalculia) and radiologically with extension of atrophy along the Sylvian fissure. This pattern of atrophy is described in previous cases of PNFA although more often in the presence of a corticobasal degeneration syndrome which Case 2 did not have. The occurrence of neologistic errors in speech may be difficult to interpret in the setting of severe speech production impairment associated with speech apraxia and/or dysarthria. However, Case 2 exhibited clear neologistic errors in written output, demonstrating that such errors represent a true jargon language disturbance in the context of a non-fluent aphasia.

One cannot argue that jargon was the only salient feature of the language disturbance in these cases (Case 2, for example, clearly made perseverative errors: see Table 6.3.2). Rather, it is proposed that the less typical finding of jargon in neurodegenerative disease (PPA) may have localising value as a clinical signature of the anatomical pattern of disease spread and may constitute a clinico-anatomical analogue of jargon in acute aphasia. While the histopathological diagnosis in these cases must remain moot, taken together, the clinical and radiological findings are consistent with the concept that involvement of the posterior superior temporal and parietal lobes may modify the phenotype of patients who present with

progressive language impairment due to a neurodegenerative disorder (PPA). The parieto-temporal distribution of disease may lead to the appearance of neologistic jargon in a proportion of such cases. In SD and PNFA posterior temporal and parietal lobe involvement is usually a late feature, whereas in LPA these regions are implicated at presentation. It is noteworthy that detailed analysis of speech errors in patients with AD (in which parietal lobe involvement is typically prominent) reveals a number of similarities with 'Wernicke's aphasia' (Nicholas et al, 1995), though aphasic disturbances including jargon may be relatively de-emphasised in the face of the more widespread deficits that accompany evolving AD.

Proposed explanations of the core defect in neologistic jargon aphasia include failure of lexical retrieval and impaired monitoring of own speech (Marshall et al, 1998). The former defect would account for failure to activate the correct item from the lexical store, while the latter defect could account for the frequent observation (as here) that patients with jargon language are frequently unaware of the errors they make. Self-monitoring is a complex neurolinguistic process with a number of elements which may break down in disease (Hartsuiker et al, 2005). It has been shown that failure of self-monitoring cannot be solely due to impaired speech comprehension and this would be consistent with the observation that most patients with primary progressive language disorders who have impaired comprehension do not produce jargon (Marshall et al, 1998).

Jargon agraphia has been described in association with a number of anatomical lesions including both left and right-sided temporal lobe atrophy (Ostberg et al, 2001; Graham et al, 2001; Shintani et al, 2001). It often occurs in conjunction with Wernicke's aphasia, consistent with involvement of different language channels as part of the core syndrome. A number of deficits have been proposed to underpin jargon agraphia: these include impaired assembly of graphemes prior to production (the 'graphemic buffer'), an impaired spelling system, and impaired access to orthographic information. While it is not possible to determine which if any of these deficits is responsible in Case 2, involvement of the dominant parietal lobe suggests that impaired access to stored orthographic representations is plausible, and might implicate a mechanism analogous to that governing spoken output. Due to the sparsity of spontaneous

speech in Case 2, it is not clear to what extent jargon agraphia signifies differential involvement of spoken and written language output pathways in this case. Unlike most reported cases of jargon aphasia and agraphia, neologistic production in Case 2 was at a single word level rather than a sentence level, arguing against a simple compensatory process (Marshall, 2006).

Failure of lexical retrieval or self-monitoring in jargon aphasia would not in itself account for the production of novel, meaningless material (neologisms) (Marshall, 2006), and the lower frequency of this syndrome in chronic degenerative compared with acute disease states also remains to be explained. Functional disconnection between stored lexical representations and the language output pathways could lead to aberrant or random activation of phonemes in neologistic jargon, due to damage involving a key interface for linking stored lexical templates with verbal output in the posterior superior temporal – inferior parietal region (Warren et al, 2005). This would be consistent with the emergence of neologisms in both Wernicke's and conduction aphasia (Kertesz et al, 1970). One would predict that degenerative disease heavily involving this posterior region should also give rise to neologisms. The present cases illustrate the importance of longitudinal assessment of language in patients with PPA and other neurodegenerative diseases, and the need for clinicians to remain alert to the emergence of features that may signal particular patterns of disease in the brain and which may therefore ultimately have diagnostic value. A larger prospective study with post mortem correlation would be required to clarify fully the anatomical correlates of this phenomenon and its histopathological associations.

It is likely that involvement of the posterior temporal – inferior parietal region is necessary but not of itself sufficient for the development of jargon in degenerative disease. In addition to the macroscopic distribution of disease, other factors such as the potential for partial functional compensation or reorganisation in progressive disease states and the microscopic distribution of tissue pathology within local cortical networks may influence the development of jargon. The study of patients with jargon may therefore provide insights into the broader and more fundamental issue of the brain mechanisms that underpin phenomenological similarities and divergences between the acute and progressive aphasias (Hillis, 2007).

6.4 Apraxia in progressive nonfluent aphasia

Apraxia can be defined as a higher order motor disorder of skilled and/or learned motor movements (Leiguarda et al, 2000). The motor control deficit in apraxia may be specific for particular movements or body parts: amongst these, apraxia of limb movements is most often described, however apraxias of the cranial musculature (orofacial apraxia: Geschwind, 1965) and apraxia of the finely coordinated movements of articulation (apraxia of speech, AOS: Ogar et al, 2005) are also well recognised. The nature and brain basis for these specific disorders of voluntary action have not been fully defined, and apraxia remains an issue of considerable neurobiological as well as clinical interest.

As discussed in previous Chapters recent studies (including that discussed in Chapter 5.2) have stressed the importance of apraxia of speech (AOS) as a defining feature of of patients with PNFA (Josephs et al, 2006; Josephs et al, 2008a): AOS is a motor speech disorder with the features of hesitancy, effortfulness with articulatory groping, phonetic errors and dysprosody (Croot, 2002; Ogar et al, 2005). As described above, PNFA may be associated clinically with parkinsonian syndromes, in particular either a corticobasal syndrome (CBS) or a progressive supranuclear palsy (PSP) syndrome. At post mortem, abnormal tau inclusions are often seen in PNFA, with the 4-repeat tauopathies of corticobasal degeneration or PSP common underlying pathologies (Josehs et al, 2006; Josephs et al, 2008a). Limb apraxia is a well-known feature of CBS (Graham et al, 2003) and can also occur with PSP syndromes (Pharr et al, 2001, Soliveri et al, 2005). Although less well studied, orofacial apraxia may also develop in CBS (Ozsancak et al, 2000; Ozsancak et al, 2004). The clinico-pathological overlap of CBS and PSP with PNFA, coupled with the central role of AOS in the PNFA syndrome, suggests that apraxia of different kinds may be clinically relevant in PNFA. Both orofacial (or buccofacial) apraxia (Tyrrell et al, 1991; Fuh et al, 1994; Sakurai et al, 1996; Sakurai et al, 1998; Roth et al, 2006) and limb apraxia (Joshi et al, 2003) have been reported in PNFA, however these associations have not been studied systematically. Furthermore, although AOS has been associated with atrophy in the left frontal lobe and insula (Ogar et al, 2006: Ogar et al, 2007; Josephs et al, 2006), the neuroanatomical correlates of the apraxias accompanying focal dementia syndromes have not been established. In this study, speech, orofacial and limb praxis were assessed in a cohort of

patients with PNFA and assessed neuroanatomical correlates of the corresponding apraxis using the semi-automated and unbiased technique of voxel-based morphometry (VBM).

METHODS

Sixteen consecutively diagnosed patients with a diagnosis of PNFA were included in the study. This was performed subsequent to the study in Chapter 5 and so does not exactly coincide with the patients in that study. The PNFA cohort comprised twelve men and four women with a mean (standard deviation) age at assessment of 72.1 (6.9) years and disease duration from symptom onset of 5.8 (2.1) years. Five patients had parkinsonian features when assessed: three had CBS, and two PSP.

Apraxia analysis

The subscores from the Apraxia Battery for Adults 2 (ABA-2, Dabul, 2000) were used as measures of apraxia. Diadochokinetic (DDK) rate score (ABA-2 subtest 1) was measured by asking patients to repeat the phrases "puh-tuh", "tuh-kuh", "puh-tuh-kuh" and "pluh-kruh-tuh" as many times as possible in 3 seconds (for two syllable phrases) and 5 seconds (for three syllable phrases) for a maximum of three trials, and the sum of the best trials from each four phrases was used as the total score. DDK rate for alternating syllables is particularly sensitive to the presence of AOS (Ogar et al, 2006) and here is used as a surrogate measure of AOS severity. Orofacial apraxia score was based on ABA-2 subtest 3B in which patients were asked to perform the following actions: stick out your tongue, whistle, puff out your cheeks, pretend to kiss, clear your throat, bite your lower lip, show me your teeth, take a deep breath and hold it, lick your lips and open your mouth. Each action was scored out of 5 (i.e. maximum score was 50): a score of 5 was assigned when the subject made an accurate, prompt, complete and readable gesture; 4 when the subject made an ambiguous or incorrect gesture, but self corrected to an accurate response, 3 when the subject's gesture was essentially correct, but crude and defective in amplitude, speed or accuracy. If the subject made no response after ten seconds, or attempted a response but was unsuccessful, the gesture was demonstrated by the examiner and scores were assigned as follows: 2 when the subject performed correctly after demonstration, 1 when the subject's gesture, after demonstration was essentally correct, but

crude and defective in amplitude, speed or accuracy and 0 when, even after demonstration, the subject was unable to perform the correct gesture. Limb apraxia score was based on ABA-2 subtest 3A in which patients were asked to perform the following gestures: make a fist, wave goodbye, snap your fingers, throw a ball, hide your eyes, make a hitch-hiking sign, make a pointing sign, salute, play the piano and scratch. Scoring was as for orofacial praxis with a maximum score of 50.

VBM analysis

VBM analysis was performed as described in Chapter 2. Linear regression models were used to examine changes in GM volume as functions of apraxia of speech (as measured by diadochokinetic rate score, ABA-2 subtest 1), orofacial apraxia (ABA-2 subtest 3B score) and limb apraxia (ABA-2 subtest 3A score) across the PPA group. Voxel intensity, V, was modelled as a function of praxis score separately for each apraxia subtype, with subject age and total intracranial volume (TIV) included as nuisance covariates. Maps showing statistically significant correlations were generated. No significant correlations were found following correction for multiple comparisons and maps are shown at an uncorrected p=0.001 significance threshold. Statistical parametric maps were displayed as overlays on a study-specific template, created by warping all native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

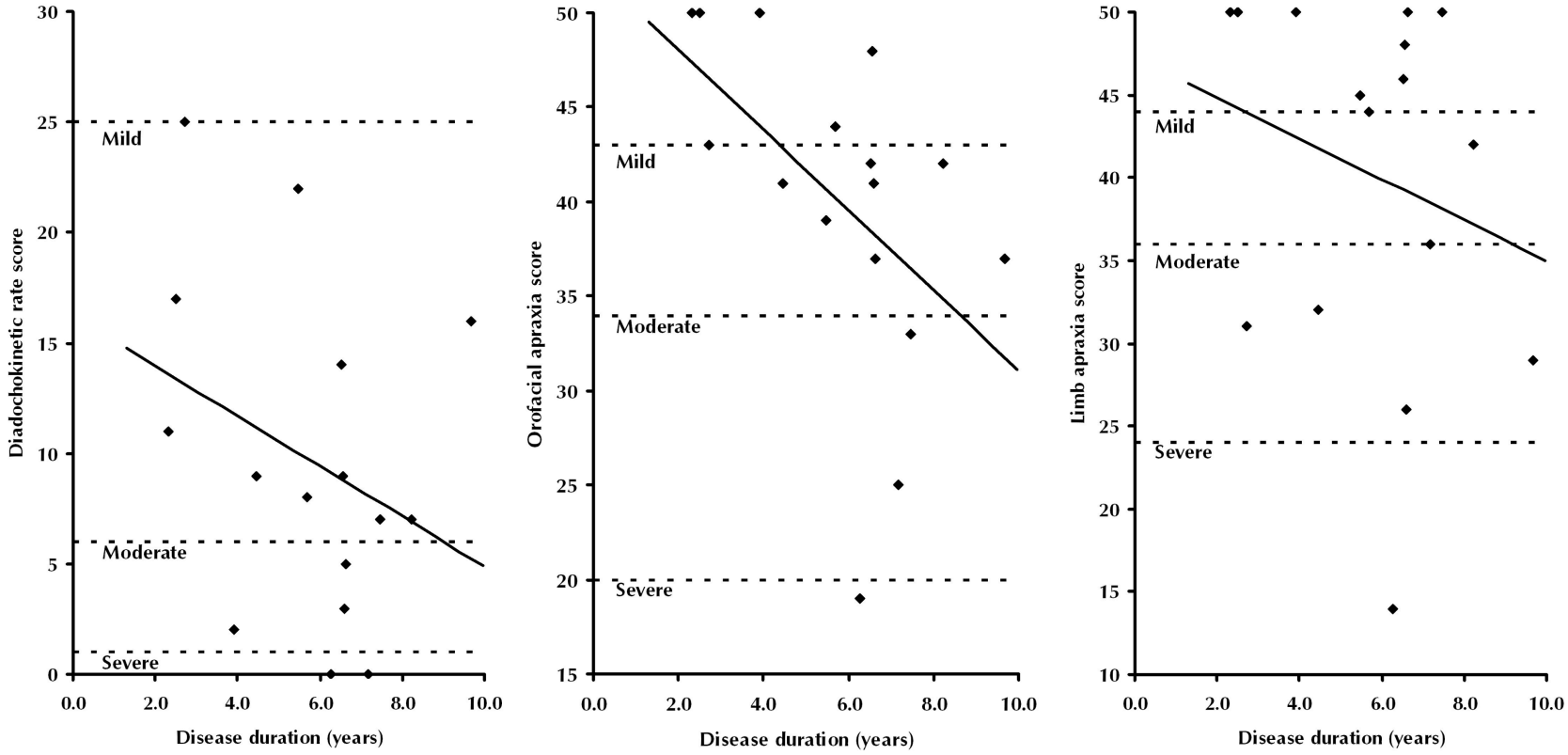
RESULTS

All patients scored in the abnormal range for DDK rate (AOS): most (69%) scored in the mildly impaired range, 19% in the moderate range and 13% in the severe range (Figure 6.4.1A). For the orofacial apraxia measure 69% of patients scored within the abnormal range (50% mild, 13% moderate and 6% severe) (Figure 6.4.1B). This included all of the patients with a parkinsonian syndrome. A substantial minority of PNFA patients had limb apraxia, 44% (7 patients) scoring in the abnormal range (Figure 6.4.1C). These seven cases included the three patients with CBS and one of the patients with PSP. For orofacial apraxia score there was a correlation with estimated clinical disease duration (p=0.04); no such correlation was found for DDK rate score (p =0.23) or limb praxis (p=0.38). Although patients were not assessed formally

for the presence of swallowing apraxia, it is noteworthy that none of the patients included in this study reported clinical dysphagia.

Figure 6.4.1

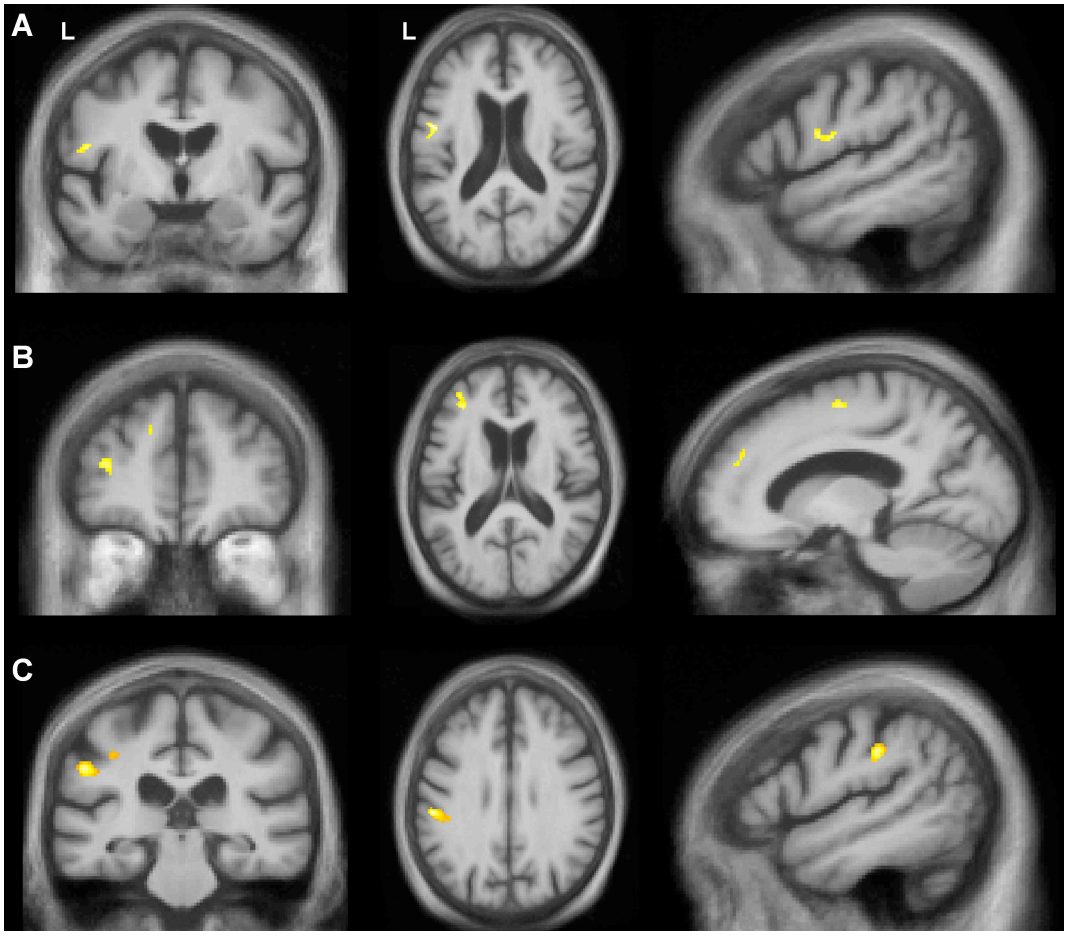
Diadochokinetic rate score (A), orofacial apraxia score (B) and limb apraxia score (C) as a function of disease duration in each of the patients. Mild, moderate and severe score cut-offs (based on ABA-2 norms) are denoted by dotted lines.



In the VBM analysis, reduced DDK rate (AOS) correlated with grey matter loss in the left posterior inferior frontal gyrus (frontal operculum) [-46, -1, 16] (Figure 6.4.2A), orofacial apraxia correlated with grey matter loss in the left inferior frontal [-32, 35, 13] and middle frontal [-30, 27, 27] gyri, and premotor and supplementary motor areas [-12, -7, 51] (Figure 6.4.2B), and limb apraxia correlated with grey matter loss within the left parietal lobe [-51, -27, 30] (Figure 6.4.2C).

Figure 6.4.2

VBM analysis correlating grey matter loss with diadochokinetic rate (apraxia of speech) score (A), orofacial apraxia score (B) and limb apraxia score (C). Statistical parametric maps (SPMs) have been thresholded at p<0.001 (uncorrected) and rendered on coronal (left), axial (middle) and sagittal (right) sections of a study-specific average group T1-weighted MRI template image in DARTEL space. In coronal and axial sections, the left hemisphere (L) is shown on the left side of the image as indicated. All sagittal sections are through the left hemisphere.



DISCUSSION

This study provides further confirmation that PNFA is associated with AOS, and reveals that orofacial apraxia occurs in the majority of cases while limb apraxia occurs in a substantial minority, particularly when there is an associated parkinsonian syndrome. Clinically, these findings suggest a need for some care in equating progressive apraxia with a particular entity such as CBS, and indicate the relevance of assessing patients presenting with PNFA for deficits in the programming of actions beyond speech articulation. The findings further demonstrate specific anatomical substrates for these different forms of apraxia in PNFA: AOS and orofacial apraxia are both associated with left inferior frontal gyrus atrophy, and orofacial apraxia is associated with additional atrophy of left middle frontal and premotor cortices, while limb apraxia is associated with more posterior atrophy in the left parietal lobe.

The findings corroborate previous work mainly in aphasic stroke indicating that orofacial apraxia often though not invariably accompanies AOS (Ogar et al, 2006; Dronkers, 1996; Hillis et al, 2004b). Anatomically, AOS and orofacial apraxia in this neurodegenerative population showed common involvement of the left inferior frontal gyrus, indicating a critical substrate that is in proximity (though non-identical) in these disorders. The neuroanatomical correlates identified here are in keeping with previous evidence (Hillis et al, 2004b; Raade et al, 1991) and implicate shared mechanisms for the programming of different kinds of complex, learned motor sequences in the left inferior frontal lobe. Orofacial apraxia may have a more distributed anatomical basis, consistent with a more generic role in orofacial motor control. The finding that the development of orofacial apraxia but not AOS or limb apraxia correlates with disease duration may speak to the anatomical organisation of these functions: strategic damage involving relatively focal cortical modules may be sufficient to produce AOS or limb apraxia, while the more distributed control of relatively simple orofacial movements implies greater neural redundancy but may be correspondingly more vulnerable to cumulative cortical insults with the advancing neurodegenerative process.

Consistent with a large body of clinical observation it was found that limb apraxia was associated with CBS (Okuda et al, 1999; Peigneux et al, 2001; Borroni et al, 2008), however

this association was not clinically specific: individual patients with PNFA and no associated parkinsonian features nevertheless exhibited limb apraxia. Anatomically, and in accord with previous anatomical evidence (Okuda et al, 1999; Peigneux et al, 2001; Borroni et al, 2008c) limb apraxia was associated with left parietal lobe atrophy, It may be that limb apraxia is indeed an early sign of the development of a parkinsonian syndrome, and longitudinal studies of PNFA cohorts will be required to resolve this. A further unsettled issue concerns the histopathological substrate for limb apraxia and for the other specific apraxias studied here, and in particular, any specificity for tau versus non-tau inclusions: it has been proposed that AOS (and indeed PNFA more generally) is closely associated with tau pathology, in particular corticobasal degeneration and PSP (Josephs et al, 2008a). This is a further important issue for future longitudinal studies with post mortem correlation.

6.5 Behavioural symptoms in primary progressive aphasia

In contrast to behavioural variant frontotemporal dementia (bvFTD) there have been relatively few studies of the phenomenology and brain basis of behavioural abnormalities in PPA (Marczinksi et al, 2004; Seeley et al, 2005; Snowden et al, 2001; Liu et al, 2004; Rosen et al, 2006). Here clinical behavioural profiles are described in each of the subtypes of PPA and the neuroanatomical correlates of behavioural change in PPA are assessed using voxel-based morphometry. Accumulating neuroanatomical evidence suggests that complex behaviours in neurodegenerative disease are mediated by fronto-temporal networks, in particular, orbitofrontal cortex (OFC) and limbic structures with a right hemisphere emphasis. Informed by this previous work, the core neuroanatomical hypothesis here was that behavioural disturbances in PPA syndromes are associated with atrophy of OFC and its functional connections.

METHODS

All 33 patients described in Chapter 5.2 and 5.3 (9 with SD, 14 with PNFA, 7 with LPA and 3 with *GRN*-PPA) were administered the Neuropsychiatric Inventory (NPI, Cummings et al, 1994), a questionnaire examining the presence and severity of the following abnormal behaviours: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, abnormal sleep and abnormal appetite/eating behaviours. The NPI score is based on use of discrete scales: for each behaviour, the score (individual behaviours /12, total /144) is the mean product of individual scores on scales of severity [1, mild through to 3, severe] multiplied by frequency [1, occasionally through to 4, very frequently]; for severity of caregiver distress scores are given from 0, no distress, through to 5, extremely distressing. Apart from one patient with *GRN*-PPA who had a cardiac pacemaker all patients also had volumetric brain MRI. Demographic data in each of the subgroups are presented in Table 6.5.1.

Table 6.5.1

Demographic data of patients

Mean (standard deviation)	SD	PNFA	LPA	GRN-PPA
Number of subjects	9	14	7	3
%Male	33.3	71.4	57.1	66.6
Age (years)	62.3 (9.0)	71.8 (6.8)	65.1 (6.4)	61.6 (9.1)
Duration (years)	5.3 (1.2)	5.3 (2.1)	4.4 (1.0)	3.9 (0.3)

Voxel-based morphometry (VBM) was performed on the patients' brain MR images as described in Chapter 2. Linear regression models used to examine differences in grey matter intensity correlating with the presence of frequently abnormal behaviours (behaviour exhibited by >25% of the PPA cohort, as indexed by the NPI). For each behaviour, subjects were classified according to whether they did or did not exhibit that behaviour and the contrast of interest was the difference between these two groups. Voxel intensity, V, was modelled as a function of group, and subject age and total intracranial volume were included as nuisance covariates. No significant differences were found following correction for multiple comparisons. Maps showing statistically significant differences between the groups were generated uncorrected at $p < 0.001$ significance level. Statistical parametric maps were displayed as overlays on a study-specific template, created by warping all native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

RESULTS

Abnormal behaviours exhibited by patients across the PPA cohort are summarised in Table 6.5.2: the mean NPI score for patients exhibiting the behaviour (an index of behaviour salience, where each score is the mean product of individual scores [behaviour severity x behaviour frequency]) and the proportion of patients exhibiting each behaviour (an index of behaviour prevalence in that patient group) are shown. The most prevalent and salient behaviours across the PPA cohort were agitation/aggression, depression, anxiety, apathy,

disinhibition, irritability/lability, and abnormal appetite/eating disorders (Table 6.5.2). Total NPI score varied between 0 (in 5 patients) and 45 and there was no relationship between total score and duration of disease, either in the PPA cohort as a whole or in any of the subgroups. All patients with SD and a majority of patients in each of the PNFA, LPA and *GRN*-PPA subgroups exhibited at least one abnormal behaviour: the overall prevalence and salience of abnormal behaviours was similar between PPA subgroups as was the overall amount of caregiver distress created by the behaviours (Table 6.5.2). Most behaviours were exhibited by all PPA subgroups and none was wholly specific for a particular subgroup. However, different profiles of behavioural change were observed between subgroups. The most prevalent behaviours in each subgroup (defined arbitrarily as behaviours exhibited by at least half the patients in that subgroup), were: in SD (in rank order) depression, irritability/lability, disinhibition, abnormal appetite/eating disorders and anxiety; in PNFA, apathy, depression and agitation/aggression; in LPA, irritability/lability, anxiety, apathy and agitation/aggression; and in *GRN*-PPA, apathy and irritability/lability (Table 6.5.2).

Table 6.5.2

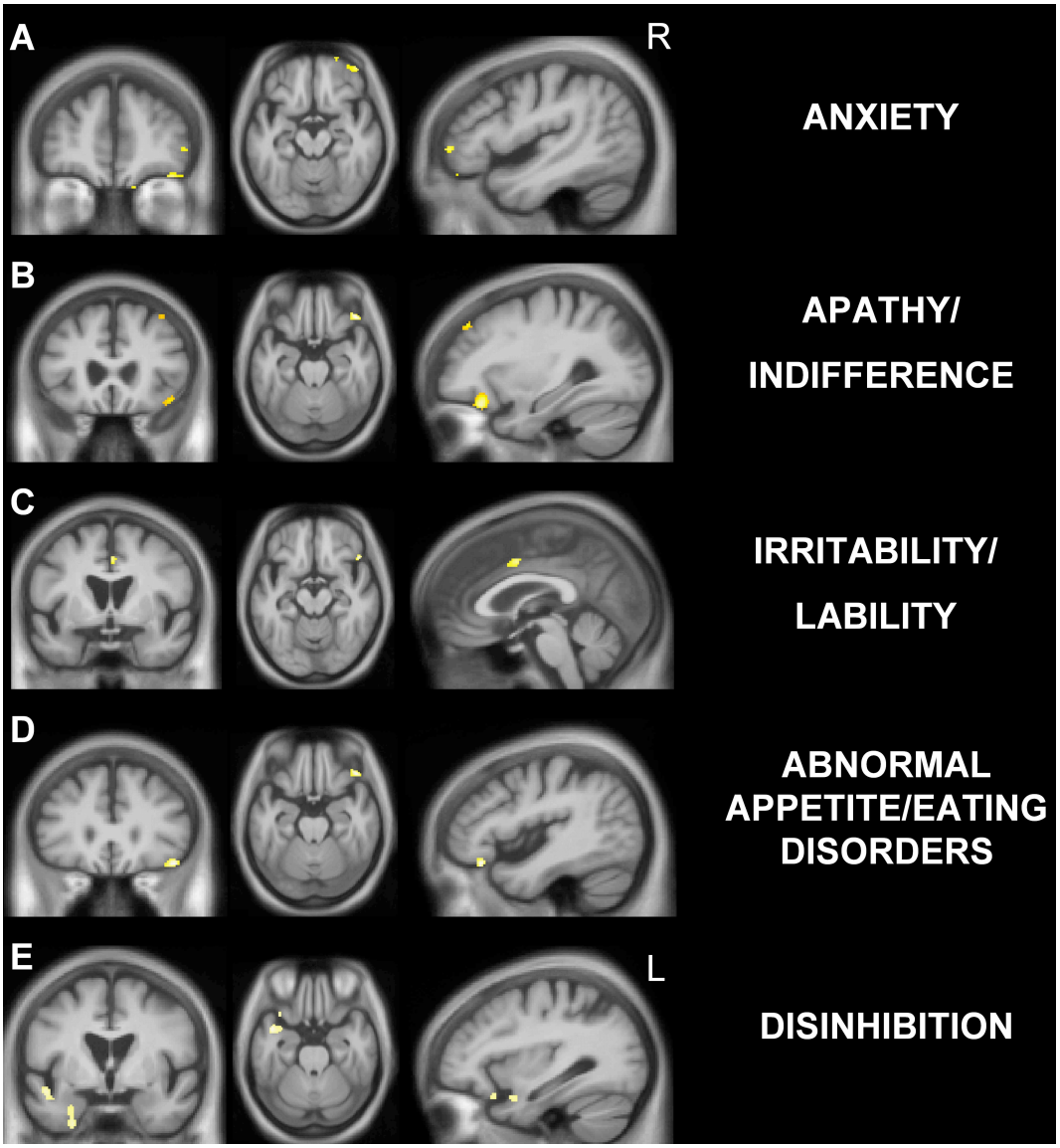
NPI mean (standard deviation, StDev) scores and percentage of patients exhibiting abnormal behaviour in all PPA patients and in subgroups. Behaviours exhibited by at least 50% of patients in each subgroup are indicated in bold.

	ALL		SD		PNFA		LPA		GRN-PPA	
	Mean (StDev)	%	Mean (StDev)	%	Mean (StDev)	%	Mean (StDev)	%	Mean (StDev)	%
Delusions	0.4 (1.3)	9	0.4 (1.3)	11	0.4 (1.6)	7	0.4 (1.1)	14	0.0 (0.0)	0
Hallucinations	0.1 (0.4)	6	0.2 (0.7)	11	0.0 (0.0)	0	0.1 (0.4)	14	0.0 (0.0)	0
Agitation/ Aggression	0.9 (1.4)	50	0.7 (1.0)	44	**0.9 (1.2)**	**50**	**1.4 (2.1)**	**57**	0.3 (0.6)	33
Depression/ Dysphoria	1.3 (1.8)	56	**1.1 (0.9)**	**78**	**1.6 (2.2)**	**57**	0.4 (0.8)	29	2.0 (3.5)	33
Anxiety	1.2 (1.8)	50	**0.8 (0.8)**	**56**	0.8 (1.6)	36	**2.6 (2.6)**	**71**	0.7 (1.2)	33
Elation/ Euphoria	0.6 (1.6)	19	0.8 (2.0)	22	0.5 (1.6)	14	0.1 (0.4)	14	1.3 (2.3)	33
Apathy/ Indifference	1.7 (2.4)	56	0.7 (1.1)	33	**2.1 (2.9)**	**64**	**2.0 (2.8)**	**57**	**1.7 (1.5)**	**67**
Disinhibition	1.3 (2.5)	38	**2.0 (2.9)**	**67**	0.7 (2.4)	14	1.7 (2.4)	43	0.7 (1.2)	33
Irritability/ lability	1.4 (1.9)	56	**1.2 (1.4)**	**78**	0.9 (2.1)	29	**2.4 (2.3)**	**71**	**1.3 (1.2)**	**67**
Aberrant motor behaviour	0.7 (1.6)	22	0.3 (0.7)	22	0.5 (1.2)	21	1.7 (2.9)	29	0.0 (0.0)	0
Abnormal sleep	0.8 (1.6)	25	1.1 (1.5)	44	0.8 (1.6)	21	0.9 (2.3)	14	0.0 (0.0)	0
Abnormal appetite/eating	2.0 (3.1)	50	**1.7 (1.6)**	**67**	2.6 (4.3)	43	1.4 (2.3)	43	1.3 (2.3)	33
Total	*12.2 (12.4)*	*88*	*11.0 (7.4)*	*100*	*11.9 (14.8)*	*79*	*15.3 (15.3)*	*86*	*9.3 (8.1)*	*67*
Caregiver distress total	*9.2 (6.0)*	*88*	*9.4 (6.1)*	*100*	*7.4 (6.0)*	*79*	*9.6 (6.8)*	*86*	*5.3 (4.60*	*67*

As the overall most prevalent abnormal behaviours were exhibited by all PPA subgroups, the subgroups were merged in the VBM analysis, in order to assess regional atrophy that correlated with the emergence of the behaviour for the PPA cohort as a whole. No VBM correlates were identified for the presence of depression or agitation/aggression ($p<0.001$ uncorrected). However partly overlapping VBM correlates were identified for other frequently abnormal behaviours ($p<0.001$ uncorrected) (Figure 6.5.1) in accord with the a priori anatomical hypotheses (Rosen et al, 2005; Peters et al, 2006; Whitwell et al, 2007b; Woolley et al, 2007; Zamboni et al, 2008; Massimo et al, 2009; Bruen et al, 2008). The presence of anxiety, apathy, irritability/lability, and abnormal appetite/eating disorders all correlated with reduced grey matter intensity in right lateral OFC (Figure 6.5.1 A-D), while the presence of disinhibition correlated with reduced grey matter in left lateral OFC [-34, 18, -21] (Figure 6.5.1 E). Additional areas of grey matter loss correlating specifically with the presence of particular behaviours were identified: the presence of apathy correlated with reduced grey matter intensity in right dorsolateral prefrontal cortex [30, 39, 37] (Figure 6.5.1 B); the presence of irritability/lability correlated with reduced grey matter intensity in right anterior cingulate [2, 2, 37] (Figure 6.5.1 C); and the presence of disinhibition correlated with reduced grey matter intensity in left anterior superior temporal gyrus [-42, 3, -18] and entorhinal cortex [-26, -3, -35] (Figure 6.5.1 E).

Figure 6.5.1

VBM analyses on grey matter regions in contrasts based on presence versus absence of abnormal behaviours as shown. Statistical parametric maps (SPMs) have been thresholded at p<0.001 (uncorrected) and rendered on a study-specific average group T1-weighted MRI template image in DARTEL space. In coronal and axial sections, the right hemisphere (R) is shown on the right side of the image. Left (L) and right (R) markers are shown for the sagittal sections.



DISCUSSION

This study demonstrates that abnormal behaviour can develop in any of the canonical subtypes of PPA. While particular PPA subtypes did not show an overall predilection to develop

behavioural abnormalities, partly differentiable profiles of behavioural impairment were associated with different subtypes. In previous work, abnormal eating patterns and disinhibition have also been associated, as here, with SD (Snowden et al, 2001; Rosen et al, 2006). However, in contrast to one earlier study using the NPI (Rosen et al, 2006) this study did not find a substantial overall increase in behavioural dysfunction in SD compared with the other groups. This may be partly attributable to the variability in disease duration, but other factors including the fact that Rosen et al, 2006 may have included patients with 'right temporal variant' SD (who have more behavioural problems) may also have contributed.

Previous studies addressing the neuroanatomical correlates of behavioural impairment in dementia have implicated a predominantly right-sided network of frontal (particularly OFC), cingulate and striatal areas in the pathogenesis of apathy, disinhibition and abnormal appetite (Rosen et al, 2005; Peters et al, 2006; Whitwell et al, 2007b; Woolley et al, 2007; Zamboni et al, 2008; Massimo et al, 2009; Bruen et al, 2008). The present data corroborate these previous findings, and underline the critical role of right OFC damage in the production of a range of abnormal behaviours in PPA. It has been proposed that OFC is involved in processing stimulus-reward associations: neuronal loss in this area leads to impaired ability to make such associations, with resulting abnormal behaviour (Viskontas et al, 2007). It has been further proposed that lateral OFC may be involved in organising behaviour toward a goal, while medial OFC evaluates the outcome (Wallis, 2007), suggesting that lateral OFC may play a generic role in the regulation of different kinds of behavioural output. Damage involving lateral OFC is therefore predicted to be associated (as here) with the emergence of a range of disorganised or context-inappropriate behaviours. The additional areas identified here may signify brain areas with more specific roles in the pathogenesis of particular abnormal behaviours, consistent with previous clinical studies and with emerging concepts of the cerebral organisation of these behaviours: dorsolateral prefrontal cortex damage has previously been linked with apathy (Zamboni et al, 2008), anterior cingulate dysfunction has been associated with emotional lability (Green et al, 2007), and entorhinal cortex participates in cerebral networks that mediate adaptive avoidance behaviours (Charney et al, 1996).

The issue of cerebral lateralisation is more problematic: neuroanatomical correlates of abnormal behaviour, in the present and in previous studies, are predominantly located in the right hemisphere, however disinhibition here correlated with damage in a left-sided frontotemporal network. Disinhibition might result from impaired ability to make affect-incongruent responses, a role attributed to left OFC in normal subjects (Roelofs et al, 2009). Clinically, the present findings suggest that the primacy of right hemisphere damage in the pathogenesis of abnormal behaviour is relative rather than absolute. It is noteworthy that those abnormal behaviours correlating with right hemisphere atrophy in the present study (anxiety, apathy, irritability, appetite) might broadly result from deranged processing of internally generated (e.g. affective) cues, while the behaviour correlating with left hemisphere damage (disinhibition) results from deranged processing of external (environmental) cues. This suggests a possible pathophysiological basis for the differential lateralisation observed that is broadly consistent with other lines of evidence in affective neuroscience (Panksepp, 2003).

The PPA syndromes are likely to overlap anatomically and histopathologically with bvFTD, in which behavioural disturbances are an early and defining feature. An anterior-cingulate fronto-insular network with projection zones including OFC has been implicated as a critical substrate in bvFTD (Seeley et al, 2007). In light of the present findings in PPA, the relative preponderance of language versus behavioural phenomenology in the various syndromic variants of FTLD might reflect differential involvement of common cerebral networks. This issue should be explored in future longitudinal studies of behavioural impairment in PPA, including techniques such as diffusion tractography and functional MRI that can capture structure:function relations in the distributed neural networks that mediate complex behaviours.

Chapter 6 summary

This Chapter builds upon the work in the previous Chapters to study in detail other behavioural and neuropsychological aspects of progressive language impairment. Single word processing problems seen in the groups were as predicted from previous studies and associated with a predominantly left-sided network of known language areas in the brain. There have been few studies of receptive prosody previously, and this preliminary study suggests that problems do occur in PPA and that this may partly account for some of the comprehension problems that occur as the disease progresses. Further studies are required in this area, particularly relating it to the underlying neuroanatomy. Neologistic jargon remains a relatively rare problem in the progressive language disorders and more studies are required in this area. This is difficult as it is likely to be a relatively late feature of the disease, and thus becomes much more difficult to study when patients are more globally impaired. However, identification of the LPA and *GRN*-PPA phenotypes which affect more posterior temporo-parietal areas likely to give rise to jargon, may lead to more descriptions of this phenomenon. Apraxias are more commonly seen in the progressive aphasias with orofacial apraxia worsening with increased PNFA disease burden. Limb apraxia occurs in subset of nonfluent patients. Behavioural problems have been studied to a small extent before in progressive language impairment, most commonly in SD with this study providing added information about the nonfluent phenotypes which have been little studied. One of the major issues with the study presented in Chapter 6.5 is the relative insensitivity of the Neuropsychatric Inventory as a measure of behavioural symptoms – better measures are needed (of which some, e.g. the Cambridge Behavioural Inventory, are starting to be studied in the neurodegenerative disease population) and more longitudinal studies of behavioural change over time are also required.

7. General conclusions: the progressive aphasias

This study provides a series of insights into the progressive aphasias from the clinical, neuropsychological, anatomical and molecular aspects of disease. As well as the canonical syndromes of PNFA and SD there is evidence of other key clinical syndromes namely LPA and the suggestion that the clinical syndrome associated with *GRN* mutations is also unique. The key features of the clinical/neuropsychological phenotypes of progressive language impairment and their anatomical, pathological and genetic associations are shown in Table 7.1.1 and Figure 7.1.1.

Table 7.1.1

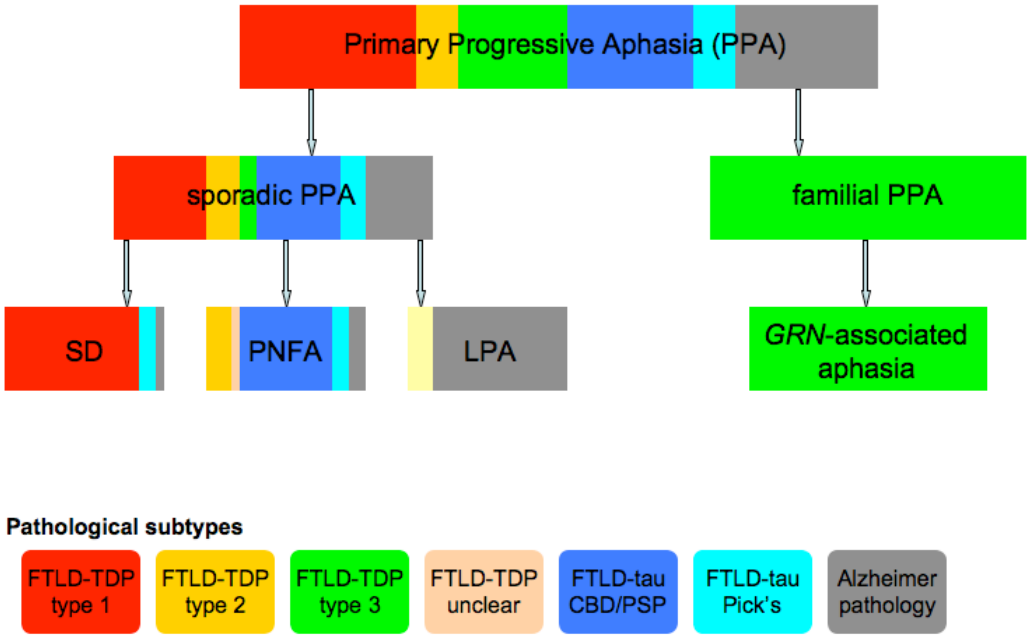
Clinical, neuropsychological, neuroanatomical and pathogenetic features of progressive language impairment

	SD	PNFA	LPA	*GRN-PPA*
Spontaneous speech	Normal rate but fluent, empty and circumlocutory Semantic errors	Slow with hesitancy, effortfulness secondary to motor speech disorder and/or agrammatism Phonetic/apraxic errors Phonemic errors	Slow spontaneous speech with word-finding pauses	Slow, sparse spontaneous speech with word-finding pauses
Semantic knowledge/ single word comprehension	Impaired secondary to verbal semantic impairment	Initially intact but in late disease becomes affected	Relatively intact	Impaired relatively early on
Word retrieval/ naming	Anomia	Initially can be normal but anomic as disease progresses	Anomia	Anomia
Grammar/ sentence comprehension	Normal initially but becomes impaired as single word comprehension deteriorates	Impaired for complex sentences	Impaired for simple and complex sentences	Impaired
Single word repetition	Normal	Impaired with phonetic/apraxic errors	Relatively intact	Impaired
Sentence repetition	Often normal initially but can make transposition errors	Can be impaired	Impaired	Impaired
Motor speech impairment/ apraxia of speech	None	Present	None	None
Reading	Surface dyslexia	Phonological dyslexia	Phonological dyslexia	Deep/ phonological dyslexia

Other cognitive domains involved	Non-verbal semantic impairment, can develop object agnosia or prosopagnosia	Can later develop dominant parietal impairment (dyscalculia, limb apraxia) particularly if associated with CBS	Phonological memory deficit and therefore poor forwards digits span. Early dominant parietal impairment and verbal memory deficit	Early dominant parietal impairment
Behavioural symptoms	Disinhibition, appetite change, depression	Apathy, depression, agitation/aggression	Anxiety, irritability/lability	Apathy, irritability/lability
Neurological examination	Usually none	Can be associated with a parkinsonian syndrome or rarely motor neurone disease	Usually normal	Usually normal but can be associated parkinsonian syndrome
Neuroanatomy (predominant areas of atrophy)	Asymmetrical anteroinferior temporal lobe involvement With spread to frontal and anterior cingulate areas (also parietal particularly when associated with Pick's disease)	Asymmetrical left inferior frontal and insula atrophy With spread to middle and superior frontal areas, temporal lobe, particularly superiorly and anterior parietal lobe	Asymmetrical left greater than right temporo-parietal junction and hippocampal atrophy With spread more anteriorly in the temporal lobe and posterior cingulate involvement	Asymmetrical left greater than right fronto-temporo-parietal lobe atrophy With spread throughout the left hemisphere and then right hemisphere involvement.
Pathogenetic associations	FTLD-TDP type 1 >> Tau-positive Pick's disease + few reports of AD pathology	Tau-positive pathology i.e. CBD, PSP, Pick's disease >> FTLD-TDP pathology + few reports of AD pathology	AD >> FTLD-TDP pathology	FTLD-TDP type 3 pathology *GRN* mutations

Figure 7.1.1

Clinico-pathological and clinico-genetic associations in primary progressive aphasia. PPA as a syndrome has heterogeneous genetic and pathological associations. However, the importance of subtyping PPA is shown by the third row of boxes which show in a schematic manner the pathological associations with SD, PNFA, LPA and with the familial GRN-associated form of PPA, where one pathological subtype tends to dominate. Each of the pathological subtypes are indicated by a separate coloured box: FTLD-TDP types 1 to 3 or type unclear if subtyping had not been performed, FTLD-tau (corticobasal degeneration, CBD; progressive supranuclear palsy, PSP; and Pick's disease), and Alzheimer pathology.



Importantly, this study also opens up two further important avenues of research in the progressive aphasias: firstly, a possible reclassification of the disorders in terms of the underlying proteinopathy which would allow patients with progressive language impairment to be entered into trials of disease-modifying treatment targeted at specific proteins and secondly, linking the underlying proteinopathy to the pathophysiological process occurring in these disorders which would allow insight into how neurodegenerative disorders occur and spread throughout the brain.

The classification of the progressive aphasias by clinical/neuropsychological phenotype has been controversial amongst different research groups with some lumping all patients with

progressive language impairment together into one group called primary progressive aphasia. It is clear however from previous research reviewed here and the work in this study that PPA can be split into clinical/neuropsychological subtypes. This study suggests there are at least four subtypes but further work is required to support this work. Perhaps one way of overcoming such disagreements between PPA researchers is to primarily reclassify PPA at a different level, that of the underlying pathological and genetic basis. Such a classification is outlined in Table 7.1.2.

Table 7.1.2

Pathological/genetic classification of the progressive aphasias

Pathological/genetic classification of progressive language impairment	**Definitive or probable diagnosis**	**Likely diagnosis**
FTLD-TDP type 1	No diagnostic test available	Asymmetrical pattern of atrophy or hypometabolism limited to anterior/inferior temporal lobe on MRI/PET/SPECT
FTLD-TDP type 2 (not studied here)	No diagnostic test available	Presence of motor neurone disease (type 2 or 3)
FTLD-TDP type 3 (mostly due to progranulin mutations)	Testing for progranulin mutations or progranulin ELISA No diagnostic test for non-*GRN* cases	Presence of motor neurone disease (type 2 or 3)
CBD	No diagnostic test available	Presence of a corticobasal syndrome
PSP	No diagnostic test available	Presence of a progressive supranuclear palsy syndrome
Pick's disease	No diagnostic test available	None
Alzheimer's disease	Positive PIB-PET scan or characteristic CSF biomarker profile (high tau/low Aβ42)	-

As can be seen from Table 7.1.2, the ability to classify patients pathogenetically is currently difficult. However, patients with AD pathology can be identified if a PIB-PET scan is available or diagnosed with good sensitivity and specificity if CSF biomarkers of tau and Aβ42 are available. This diagnosis will become easier when a ligand with a longer half-life than PIB

becomes available (and therefore obviate the need to be a centre with a cyclotron) or when more pathologically-based studies of CSF biomarkers show high sensitivity and sensitivity for a diagnosis of AD (and the availability of the biomarkers become more widespread). This leaves the patients with the FTLD pathologies of tau and TDP-43 pathology and the difficulty of separating these two groups either into just tau versus TDP-43 or into the six subtypes (3 FTLD-TDP pathologies, type 1 to 3, and 3 tau-pathologies, CBD, PSP and Pick's disease). There is currently no molecular PET imaging for tau or TDP-43 proteins nor any specific serum or CSF biomarkers (although there are small studies of serum TDP-43 levels which requires further investigation: (Foulds et al, 2008; Foulds et al, 2009). There are however some supportive features which will give a variable sensitivity and specificity for either tau or TDP-43 pathology. The presence of a progressive supranuclear palsy syndrome is suggestive of tau pathology (although not 100% as some very rare cases have been described with ubiquitin-positive inclusions (Paviour et al, 2004) and as shown in Chapter 5 it is often not present early on). The presence of an apraxia of speech is also likely to be suggestive of tau pathology (Josephs et al, 2006). A corticobasal syndrome is likely to be due to tau pathology but it is less specific than a PSP syndrome as there are a number of cases described with TDP pathology in association with progressive language impairment. With FTLD-TDP, a diagnosis of a progranulin mutation is definitive for such pathology but it may be easier (and cheaper) to initially perform a progranulin level by ELISA which has recently been shown to be highly predictive of progranulin mutations (Coppola et al, 2008; Finch et al, 2008). The presence of motor neurone disease is also predictive of TDP pathology (either type 2 or 3) but may occur later in the disease after the presentation with language impairment. The presence of the classical SD imaging pattern of asymmetrical anteroinferior temporal lobe atrophy also has relatively high specificity and sensitivity for FTLD-TDP type 1 pathology. In summary, a combination of neurological, neuropsychological, imaging and CSF (or PIB-PET) data currently can provide an imperfect pathogenetic classification of the progressive aphasias but it is likely that with improved molecular imaging and CSF techniques this will improve.

One of the questions that arises from the classification of the progressive aphasias as proteinopathies is how such protein deposition in neurones actually causes progressive

language impairment. This topic was briefly touched upon in Chapter 1 when discussing the differences between these disorders and the acute, particularly vascular, aphasias and also, more substantially, in Chapter 4.3 discussing the differences between patterns of atrophy in *GRN* and *MAPT* mutations. It is likely that the clinical/neuropsychological phenotype of progressive language disorders arises from dysfunction with a specific neural network: both pathological and neuroimaging research has suggested that this is the case for bvFTD, ascribed to selective vulnerability of von Economo neurons within a frontal-insula-anterior cingulate network (Seeley et al, 2006; Seeley et al, 2007; Seeley, 2008; Seeley et al, 2008). Pathophysiological networks are less clear for the progressive language disorders but there are suggestions arising from this work. As discussed in Chapter 4.3, the different mutations and pathologies can have variable clinical/neuropsychological presentations suggesting that molecular lesions do not specify a precise initial anatomical locus of brain damage. However, the evidence here suggests that, once initiated, the pattern of disease evolution that can occur in the different pathologies is constrained by the underlying molecular abnormality. TDP type 1 and type 3 and also the tau-positive pathologies have been shown to be associated with asymmetrical atrophy. Although spread occurs to the other hemisphere it appears to spread more easily through the same hemisphere (the evidence in Chapter 3.4 and 4.4 suggestive of increasing asymmetry of atrophy as the disease progresses) and the extent and time from disease onset when the right hemisphere becomes involved differs between the different pathologies. The extent of symmetry (or asymmetry) is likely to depend on whether the disease spreads preferentially through long-range association tracts (which appears to be the case in most of these pathologies) rather than short-range interhemispheric connections (which seems to be the case in *MAPT* mutations). This suggests that the long-range association tracts in the left hemisphere which are well-known to be part of the language neural network (e.g. the superior and inferior longitudinal fasciculi) are vulnerable to the deposition of certain proteins within the cells in that network. Spread of disease through a particular vulnerable network predicts the likely clinical phenotypes associated with a particular pathology e.g. CBD pathology, when it affects the left hemisphere is likely to cause PNFA if it affects the anterior section of the fronto-parietal network or a corticobasal syndrome if it affects the posterior part. This also predicts that there is a right hemisphere mirror network which can also be affected

initially causing bvFTD if the anterior part of the network is affected and corticobasal syndrome if the posterior part is affected first. These predictions are easily testable and there is preliminary evidence from the different phenotypes seen with CBD pathology that this is the case. Further pathological and imaging studies (e.g. resting state functional MRI or tractography) are required to fully identify such networks and the vulnerable neuronal populations in the different pathologies.

This thesis therefore provides neurological, neuropsychological and imaging data with related genetic and pathological information that can provide greater insights into the natural history and classification, and therefore pathophysiological basis of the neurodegenerative disorders that cause primary progressive language impairment. Ultimately, this information will hopefully be useful in moving the neuroscientific community further forwards in understanding these conditions, so that treatments can be discovered, trialled and finally used in clinical practice to treat, and eventually cure the progressive language disorders.

8. References

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9. Division of labour for experimental work

Chapter 3

The author was involved in designing, running and performing the cortical thickness Freesurfer pipeline and also in the statistical analysis. Dr Gerard Ridgway provided statistical support for the cortical thickness analysis. The author was involved in designing and performing the longitudinal imaging study including performing the temporal lobe and hemisphere segmentations and instituting the BSI and SIENA methods. Brain segmentations were performed mostly by Elizabeth McNaught (Gordon). Ventricle segmentations were performed by Shona Clegg.

Chapter 4

The author was involved in designing and performing the genetic study including collecting DNA samples and devising the modified score of heritability. The VBM studies were designed and performed by the author with statistical support from Dr Gerard Ridgway. The laboratory genetic analyses were performed by Dr Simon Mead, James Uphill, Jonathan Beck, Dr Adrian Isaacs, Professor John Hardy, Jana Vandrovcova, Rita Guerreiro and Dr Rohan de Silva. The laboratory pathological analyses were performed by Dr Tamas Revesz, Dr Janice Holton and Dr Tammaryn Lashley.

Chapter 5

The neurolinguistic battery of tests used in this Chapter was designed by the author with the help of Professor Elizabeth Warrington and Dr Jason Warren. The neurolinguistic testing and some of the background neuropsychological testing were performed by the author. The rest of the background neuropsychological testing was performed by Julia Hailstone and Johanna Goll. The imaging studies were designed and performed by the author. The detailed single case studies were designed and performed by the author with the help of Professor Elizabeth Warrington, Dr Jason Warren and Dr Sebastian Crutch. The midbrain volume analysis in the PSP study was performed by Dr Dominic Paviour.

Chapter 6

The imaging analyses were designed and performed by the author. The prosodic processing study stimuli were designed by the author with the help of Dr Jason Warren.

10. Acknowledgements

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11. Publications arising from this thesis

1. Introduction

- Rohrer JD, Knight WD, Warren JE, Fox NC, Rossor MN, Warren JD. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain. 2008;131(1):8-38.

3. Neuroanatomy of language impairment in FTLD

- Rohrer JD, Fox NC. Neuroimaging of primary progressive aphasia. European Neurological Journal. 2009;1(1).
- Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, Ourselin S, Fox NC. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. Neurology. 2009;72(18):1562-9.
- Rohrer JD, McNaught E, Foster J, Clegg SL, Barnes J, Omar R, Warrington EK, Rossor MN, Warren JD, Fox NC. Tracking progression in frontotemporal lobar degeneration: serial MRI in semantic dementia. Neurology. 2008;71(18):1445-51.
- Rohrer JD, Ridgway GR, Modat M, Kittus R, Blair M, Frost C, Rossor MN, Ourselin S, Fox NC, Warren JD. Tracking progression with serial MRI in the language variants of frontotemporal lobar degeneration. Submitted.

4. Genetics and pathology of language impairment in FTLD

- Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IR, Warren JD, de Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73(18):1451-6.
- Beck J∗, Rohrer JD∗, (∗joint first author) Campbell T, Isaacs A, Morrison KE, Goodall EF, Warrington EK, Stevens J, Revesz T, Holton J, Al-Sarraj S, King A, Scahill R, Warren JD, Fox NC, Rossor MN, Collinge J, Mead S. A distinct clinical, neuropsychological and

radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain. 2008;131(3):706-20.

- Rohrer JD, Warren JD, Omar R, Mead S, Beck J, Revesz T, Holton J, Stevens JM, Al-Sarraj S, Pickering-Brown SM, Hardy J, Fox NC, Collinge J, Warrington EK, Rossor MN. Parietal lobe deficits in frontotemporal lobar degeneration caused by a mutation in the progranulin gene. Arch Neurol. 2008;65(4):506-13.
- Rohrer JD, Ridgway GR, Modat M, Ourselin S, Mead S, Fox NC, Rossor MN, Warren JD. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. Neuroimage. 2010;53(3):1070-6

5. Heterogeneity of the nonfluent progressive aphasia variants

- Rohrer JD, Rossor MN, Warren JD. Syndromes of nonfluent primary progressive aphasia: a clinical and neurolinguistic analysis. Neurology, 2010;75(7):603-10.
- Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, Mead S, Beck J, Mummery C, Ourselin S, Warrington EK, Rossor MN, Warren JD. Progressive logopenic/phonological aphasia: Erosion of the language network. Neuroimage. 2010;49(1):984-93.
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- Rohrer JD, Rossor MN, Warren JD. Alzheimer pathology in primary progressive aphasia. Neurobiology of Aging, 2010; [Epub ahead of print].
- Rohrer JD, Paviour D, Bronstein AM, O'Sullivan SS, Lees A, Warren JD. Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: A neuropsychological and neuroimaging analysis. Mov Disord. 2010;25(2):179-88

6. Further neuropsychological and behavioural studies

- Rohrer JD, Sauter D, Scott S, Rossor MN, Warren JD. Receptive prosody in nonfluent primary progressive aphasias. Submitted.
- Rohrer JD, Rossor MN, Warren JD. Neologistic jargon aphasia and agraphia in primary progressive aphasia. J Neurol Sci. 2009 Feb 15;277(1-2):155-9.
- Rohrer JD, Rossor MN, Warren JD. Apraxia in progressive nonfluent aphasia. J Neurol 2010;257(4):569-74
- Rohrer JD, Warren JD. Phenomenology and anatomy of abnormal behaviours in primary progressive aphasia. J Neurol Sci. 2010;293(1-2):35-8.

7. General conclusions: the progressive aphasias

- Rohrer JD, Schott JM. Primary progressive aphasia - defining genetic and pathological subtypes. Current Alzheimer Research, in press.